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BRITISH MEDICAL JOURNAL

LONDON SATURDAY SEPTEMBER 2 1961

POLIOMYELITIS-LIKE DISEASE IN 1959

A COMBINED SCOTTISH STUDY*

During the early summer months of 1959 an unusual epidemic situation was observed in Scotland. Although many patients were admitted to hospital with a provisional diagnosis of "meningitis" or "poliomyelitis" and presented a clinical picture which suggested a virus agent as the cause, from none of them was a poliovirus isolated. This was not a local phenomenon, for the experience was common to the Western, Eastern, and South-Eastern Hospital Regions of Scotland. These regions contain the major infectious disease units serving the large population areas centring on the Clyde Valley, Dundee, and Edinburgh. These units have combined to describe the circumstances.

Material and Methods

Selection of Cases

The presentation of the details of an epidemic is not difficult when the cause is a single agent which produces a readily identifiable clinical picture. In the present situation it was quickly apparent that, despite a broad similarity in the symptoms and signs, several viral agents were responsible. It seemed undesirable, if a correct assessment of the situation was to be made, to concentrate on one particular agent, on one clinical presentation, or even on too restricted a period of time, since an attempt to survey the whole might have value to clinicians and virologists in showing our success as well as our failure. All of the cases admitted to the participating clinical units during 1959 which qualified for the rather vague title "poliomyelitis-like illness" were reviewed. This term was intended to include all those patients in whom poliomyelitis, in either its paralytic or non-paralytic form, was at least considered in the differential diagnosis on admission to hospital, even if, at a comparatively early stage thereafter, this diagnosis was discarded. The total number of patients included in the survey was 310, from the majority of whom specimens had been submitted to the virus laboratories. The distribution of the cases among the different hospitals was as follows:

Glasgow Area	Belvidere Hospital	39
	Ruchill Hospital	80
	Royal Hospital for Sick Children	18
Environs of Glasgow	Ayrshire Central Hospital	4
	Gateside Hospital (Greenock)	15
	Infectious Diseases Hospital (Paisley)	7
	Strathclyde Hospital (Lanarkshire)	61
Dundee Area: King's Cross Hospital		43
Edinburgh Area: City Hospital		43

Classification of Cases

All of the clinicians used the same standard form. On the basis of recorded clinical data, a senior clinician without knowledge of the results of virus examination classified the cases into the following three categories:

Category A.—Patients in whom muscle paralysis was a prominent feature, whose clinical illness could not easily or readily be distinguished from poliomyelitis, and whose initial specimen of cerebrospinal fluid was abnormal.

Category B.—Patients in whom paralysis was absent on admission but whose signs and symptoms indicated an acute meningitis and from whom an abnormal cerebrospinal fluid was obtained. From this category cases of bacterial meningitis were excluded.

Category C.—Patients who did not conform to the other two categories. This rather heterogeneous group of cases was retained, even though they did not always fit into the epidemic group, to meet the possibility of a more diverse clinical pattern of illness.

Virological Methods

An admission specimen of stool and/or paired samples of blood serum for virological examination were available from all but 20 of the patients. Specimens from patients in the Dundee and Clyde Valley areas were examined at the Glasgow University Virus Laboratory in Ruchill Hospital; those from the Edinburgh area at the Bacteriology Department of Edinburgh University.

A detailed account of the methods used in Glasgow will be published elsewhere. In brief, from each stool sample three aliquots of a 20% suspension were prepared. These were kept frozen until tested. Primary tests consisted of inoculation into stationary tissue cultures of rhesus monkey kidney and of human thyroid (Duncan, 1960a). Aliquots of stools from which viruses had been isolated in either of these tissues were tested in human amnion cultures for comparative purposes

*The clinicians taking part in this study were:—*Dundee:* King's Cross Hospital, Drs. W. M. Jamieson and Mary R. Kerr. *Edinburgh:* City Hospital, Drs. A. Joe and G. Sangster. *Glasgow:* Belvidere Hospital, Drs. M. Fletcher, P. McKenzie, and A. L. K. Rankin; Royal Hospital for Sick Children, Dr. G. C. Arneil, Professor Stanley Graham, Drs. J. H. Hutchison and R. A. Shanks; Ruchill Hospital, Professor T. Anderson, Drs. J. H. Lawson and J. Stevenson. *Greenock:* Gateside Hospital, Dr. R. Lamb. *Irvine:* Ayrshire Central Hospital, Drs. A. Mechie and M. J. Millar. *Motherwell:* Strathclyde Hospital, Dr. R. S. Dewar. *Paisley:* Infectious Diseases Hospital, Dr. W. Napier.

Virological tests were performed by Dr. F. L. Constable (Bacteriology Department, University of Edinburgh) and by Drs. Eleanor J. Bell, I. B. R. Duncan, N. R. Grist, and Constance A. C. Ross (University Virus Laboratory, Ruchill Hospital, Glasgow).

The paper was prepared by Dr. Joan B. Landsman (epidemiologist and secretary) and Dr. N. R. Grist in consultation with Professor T. Anderson.

(Duncan and Bell, 1961). Agents isolated in tissue cultures were identified by neutralization tests with immune sera prepared in rabbits. For detection of Coxsackie A viruses, suckling mice were inoculated intraperitoneally with stool extracts from cases of paralytic disease, aseptic meningitis, and encephalitis from which no virus had been isolated in tissue culture. Agents isolated in suckling mice were identified by the histological appearances of paralysed mice and by haemagglutination-inhibition, complement-fixation, and neutralization tests (Grist, 1960). Sera from patients were stored at −20° C. and submitted to complement-fixation tests for mumps, herpes, lymphocytic choriomeningitis, adenovirus, louping ill, and leptospirosis (Ross and Ives, 1960). Positive serological diagnoses were based on fourfold or greater rising titres shown by consecutive sera from the same patient tested simultaneously.

In Edinburgh basically similar methods were used, but tests for louping ill were not done and monkey kidney and HeLa tissue cultures only were used for virus isolation.

Poliomyelitis Immunization

A special effort was made to determine the exact state of poliomyelitis immunization in a group of cases admitted to some of the hospitals in the Western Region. Since information about such procedures recorded in the patient's case sheet on the basis of parents' statements was of doubtful accuracy, both the family doctor and the medical officer of health in the area in which the patient resided were asked for information on any prophylactic inoculations the patient had received. The request was presented in an explanatory letter accompanied by a standard form to be completed and returned.

Results

The series totalled 310 patients, from 20 of whom no specimens were available for examination. Among the 290 investigated by laboratory methods (see above), 174 infections were identified in 168 individuals. Three main virus agents were encountered—namely, Coxsackie A7, Coxsackie B5, and Frater virus (Duncan, 1960b). These accounted for 116 of the 174 infections; the remainder comprised such infections as mumps (14 cases), other E.C.H.O. viruses (13), leptospirosis (8), adenoviruses, Coxsackie group B viruses not type 5 and unidentified viruses (5 cases each), other Coxsackie group A viruses (4), herpes simplex (2), poliovirus type 1 and louping ill (each 1 case). Two infections were identified in four cases, and in one other case three infecting agents were found.

TABLE I.—*Clinical Categories and Laboratory Results*

Clinical Category	Total Patients	Coxsackie A		Coxsackie B		E.C.H.O. Virus		Other Infections*	No Infection Identified†
		Type 7	Other	Type 5	Other	Frater	Other		
A	13	7	—	—	—	1	—	2	3
B	271	26	4	12	4	62	11	30	126
C	26	1	—	3	1	4	2	4	13
Total	310	38		20		80		36	142

* See text.
† No specimens were available from 20 patients (17 Category B, 3 Category C).

A virus infection was thus defined in just over half the cases. Tables I, II, and III show some of the main features which are later referred to in greater detail. In each of the main virus groups there was a roughly 2:1 excess of males; the excess was specially marked under the age of 5 years. In the series as a whole there were 90 patients in the first five years of life, 79 in the second, and 57 in the third; over the age of 15 years 84 cases were observed. This concentration of cases in childhood might suggest an aetiological agent which was not new to the community, but, as indicated later, the age distribution was not uniform within the different aetiological groups. As would be expected, the majority of patients fell within category B—that is, they conformed to the clinical picture usually designated "aseptic meningitis." Although patients have been included from every month of the year, almost 80% of the total were seen between May and October inclusive. Most of the interest, however, arises from the diverse virus aetiology, and accordingly each of the main agents is dealt with separately.

TABLE III.—*Symptoms at Onset*

Symptom	Coxsackie A7	Coxsackie B5	Frater	No Agent
Headache	17	13	62	101
Vomiting	20	12	59	79
Fever	19	9	35	72
Irritability	10	1	11	20
Anorexia	19	6	28	45
Listlessness	16	3	21	22
Limb weakness	3	1	2	9
Pain: Abdomen	—	—	5	12
Pain: Back	5	5	2	21
Pain: Limb	—	—	5	21
Pain: Neck	5	2	7	20
Photophobia or pain in eyes	0	2	13	20
Sore throat	2	1	2	8
Cough	2	0	0	2
Convulsions or twitching	4	0	0	4
Drowsiness	2	1	4	6
Total cases	34	15	67	122

Coxsackie A Infections

These viruses were isolated from 38 cases: in 34 the type was A7. The four exceptions were two type A9 and two of unidentified type.

The 34 Coxsackie A7 cases clearly showed an epidemic grouping, the first patient having been seen in April and the last in September, with the peak of occurrence in June and July (Table IV). Curiously—

TABLE II.—*Age-Sex Distribution. Main Virus Groups + Unidentified*

Age Group (Years)	Coxsackie A Virus				Coxsackie B Virus				E.C.H.O. Virus				No Agent Identified			
	Type 7		Other		Type 5		Other		Frater		Other					
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M*	F*
–1	5	—	—	—	1	—	2	—	1	—	1	—	4	2	4	1
–5	11	8	2	—	2	1	1	—	10	1	4	—	12	9	—	2
–10	4	3	2	—	2	3	1	—	13	7	4	—	22	2	4	—
–15	1	1	—	—	—	—	1	—	16	3	1	—	13	13	3	2
–25	1	—	—	—	3	2	—	—	8	2	—	1	12	11	1	1
25+	—	—	—	—	1	—	—	—	2	4	—	2	11	11	1	1
Total	22	12	4	—	9	6	5	—	50	17	10	3	74	48	13	7

* 20 cases without laboratory examination.

Coxsackie A7 Epidemic

Month	Cases
April	1
May	3
June	9
July	9
August	7
September	5

Coxsackie A7 Symptoms

Headache was the commonest symptom, occurring in 17 cases. Vomiting, fever, anorexia, and listlessness were also frequent. Pain in the abdomen, back, limb, or neck was rare. Photophobia or pain in the eyes was absent. Sore throat, cough, convulsions or twitching, and drowsiness were rare.

Coxsackie A7 Signs

Rash was present in 5 cases. Herpes labialis was present in 2 cases. Pharyngitis was present in 3 cases. Tonsillitis was present in 2 cases. Enlarged cervical glands were present in 2 cases. Enlarged axillary glands were present in 1 case. Enlarged inguinal glands were present in 1 case. Enlarged epitrochlear glands were present in 1 case. Enlarged parotid glands were present in 1 case. Conjunctivitis was present in 1 case. Meningism was present in 1 case. Ataxia was present in 1 case. Hemiplegia was present in 1 case. Paraplegia was present in 1 case. Tremor was present in 1 case. Nystagmus was present in 1 case. Abnormal reflexes were present in 1 case.

Coxsackie A7 Cerebrospinal Fluid

Cerebrospinal fluid was examined in 31 cases. Pleocytosis was present in 25 cases. Raised protein was present in 3 cases. Raised pressure was present in 1 case.

Coxsackie A7 Duration of Illness

Duration	Cases
1 day	1
2 days	2
3 days	5
4 days	5
5 days	4
6 days	3
7 days	4
8 days	1
9 days	1
10 days	1
11 days	1
12 days	1
13 days	1

and it is interesting that this is true in each main virus group—all of the patients in the first year of life were males. Only three of the patients were over 10 years and 24 were under 5 years—a distribution which suggests that Coxsackie A7 was no newcomer to Scotland.

Coxsackie A7 infections were not seen in the Edinburgh area. Although there was no difference in the age distribution of the cases encountered in the Dundee and Clyde Valley areas, there is a suggestion that the epidemic occurred in the West a little earlier than in the East of Scotland (Table V). Indeed, it was a striking

TABLE IV.—*Month of Onset: Principal Infecting Agents and Unidentified Cases*

Month of Onset	Coxsackie A7	Coxsackie B5	Frater Virus	No Agent Identified
January	—	—	—	5
February	—	—	—	3
March	—	—	1	4
April	1	—	—	6
May	1	—	—	16
June	14	2	1	15
July	10	2	13	12
August	7	2	24	19
September	1	4	19	13
October	—	5	6	11
November	—	—	2	12
December	—	—	1	6
Total	34	15	67	122

TABLE V

Month of Onset	Clyde Valley Area	Dundee Area
April	1	0
May	1	0
June	12	2
July	3	7
August	3	4
September	0	1
Total	20	14

observation that a number of the early cases were noteworthy for their odd clinical presentation and the fact that they were grouped in a small burgh a few miles west of Glasgow.

Category A (7 Cases)

All of these cases, which closely simulated paralytic poliomyelitis, occurred in male children within the first half of the A7 epidemic period. No explanation for this concentration of paralytic cases was found from a comparison of the age-and-sex distributions in the first and second halves of the outbreak. The following are short extracts of the clinical data.

Case 1.—A boy aged 6 months was admitted to Ruchill Hospital on April 20, 1959. Apparently free from any paralysis on admission, he developed a left facial paralysis six days later. This paralysis was still present on dismissal. The child had received no injections of poliovaccine. The mother failed to bring the infant to the follow-up clinic. Coxsackie A7 virus was present in the stool on April 23.

Case 2.—A boy aged 5 years was admitted to Ruchill Hospital on May 18, 1959. On admission no paralysis was noted, but later impaired movement of right knee was seen and paralysis of right quadriceps was evident 14 days after admission. This improved during the next fortnight, but was still apparent on transfer to an orthopaedic unit. At follow-up nine months later there was no residual weakness. This child had received three injections of poliovaccine, the last four weeks prior to admission. Coxsackie A7 virus was present in the stool on May 20.

Case 3.—A boy aged 11 months was admitted to Strathclyde Hospital on June 4, 1959, severely ill with obvious paralysis of the right shoulder-girdle. There was rapid deterioration with increasing paralysis and peripheral circulatory failure, and he died six hours after admission. He had received one injection of poliovaccine 17 days previously. Coxsackie A7 virus was isolated from faeces.

Case 4.—A boy aged 3 years was admitted to Ruchill Hospital on June 5, 1959. He was not thought to have muscle weakness on the day of admission, but 12 days later involvement of the quadriceps muscles on the left side was noted. This weakness was still present on dismissal, but gradually disappeared. No weakness could be detected at follow-up examination 10 months later. The child had received three injections of poliovaccine. Virus was isolated from a stool of June 8.

Case 5.—A boy aged 2 years was admitted to Ruchill Hospital on June 11, 1959. Paralysis involved left shoulder-girdle and hand muscles, and weakness of left deltoid was still present on transfer to an orthopaedic unit and at follow-up eight months later. He had received two injections of poliovaccine. Coxsackie A7 virus was isolated from a stool on June 11.

Case 6.—A boy aged 3 years was admitted to Ruchill Hospital on June 26, 1959. Weakness in right forearm muscles (grade 2) on admission. Later noted to have weakness in muscles of right leg and to drag right foot on attempting to walk. All muscle groups showed good contractions 14 days later, and on dismissal at 21 days no muscle weakness could be detected. Poliovaccine injections were not given until after his illness. Coxsackie A7 virus was found in a stool on June 29.

Case 7.—A boy aged 10 months was admitted to King's Cross Hospital on July 7, 1959. On admission he was found to have impaired movement of left shoulder-girdle muscles. There was gradual improvement during next six weeks, and condition was normal on dismissal. There was a history of two injections of poliovaccine. Virus was isolated from a stool obtained on July 9.

It will be noted that in three of these patients muscle weakness was not observed on admission but paralysis appeared from 6 to 14 days later. In a further three muscle weakness was of very short duration and had disappeared by the time of dismissal. That very widespread damage of nerve cells can occur is apparent from Case 3 where histological examination showed the presence of extensive lesions (Grist and Roberts, to be published).

Category B (26 Cases)

These patients showed, in varying degree, evidence of spinal stiffness indicative of meningitis, and lumbar puncture revealed an abnormal fluid.

Too much stress cannot be placed on the comparison of small numbers, but it would seem that the Coxsackie A7 cases were admitted a little later in the course of illness than the E.C.H.O. cases, and, as Table III shows, headache and vomiting were less frequent, and neck stiffness was more marked, in the Coxsackie A7 group. Pain on movement of the eyes and photophobia were not noted in A7 cases, but convulsions or severe twitchings were seen. The latter, together with the evidence that this virus could produce a paralytic infection, suggest that widespread neuronal damage may occur.

Category C (1 Case)

Case 8.—A girl aged 13 years was admitted to Ruchill Hospital on June 10, 1959, with a history of recurring headaches and blurring of vision for two to three months and of lethargy for one month. Headache had increased in severity on the day before admission and was accompanied by vomiting. Signs of meningeal irritation were not found, and the only positive feature on admission was tenderness over the *left* frontal sinus and antrum. The C.S.F. cell count was 2/c.mm., protein 20 mg., and sugar 66 mg./100 ml. *X*-ray examination of sinuses showed

slight thickening of the *right* antral mucosa. Pyrexia from 99 to 102.6° F. (37.2–39.2° C.) continued for 48 hours after admission, but progress was uneventful and she was discharged after 14 days. The diagnosis made on dismissal was migrainous headaches. Coxsackie A7 virus was isolated in suckling mice from a stool specimen of June 12. E.E.G. on June 24 was normal.

Coxsackie B Infections

Coxsackie group B viruses were isolated from 20 cases; 15 belonged to type B5 and four to type B2. Another Coxsackie virus remained untyped. The patient from whom it was isolated had serological evidence of leptospirosis, with a normal cell count (Category C case). These infections were distributed fairly evenly throughout the period May–October, with the largest monthly total (5 B5 and 1 B2) in October. The age distribution was predominantly under 10 years (13 of the 19).

Category B (16 Cases)

Transient weakness of a limb was noted in one patient.

Case 9.—A boy aged 9 months was admitted to Ruchill Hospital on October 14, 1959, with a history of recent respiratory infection, with cough and nasal catarrh. For two nights before admission he had been restless. His parents noticed that the child was not using his left arm on the night before admission and had taken him to a casualty department, where poliomyelitis was suspected. No poliovaccine injections had been given. The child was afebrile and did not seem to be ill. Physical examination was negative apart from weakness and flaccidity of the left arm. Lumbar puncture showed 21 cells/c.mm. in the C.S.F.; protein 15 mg. and sugar 64 mg./100 ml. Two days after admission weakness had disappeared. The child was discharged after 14 days. Coxsackie B2 virus was isolated from a stool obtained on October 15.

The clinical data did not differ greatly from those in the other main aetiological groups. Of the 15 type B5 cases, 11 were admitted in the first three days of illness. Headache was often noted, but there was little comment on irritability. The cell counts and protein levels in the C.S.F. were essentially similar to those in the other aetiological groups.

Category C (3 Cases Typed)

Case 10.—A girl aged 7 years was admitted to City Hospital on September 30, 1959. Sudden onset with headache, vomiting, and sore throat; only slightly ill; C.S.F., 0 cells; protein 75 mg. and sugar 145 mg./100 ml. Recovery appeared complete by the second day in hospital. Coxsackie B5 virus was isolated from the stool.

Case 11.—A youth of 18 was admitted to City Hospital on October 4, 1959. He had been admitted to a general hospital on September 29 with a history of headache and neck stiffness after having been struck on the back of the head with a football. Pyrexia and neck rigidity disappeared within 24 hours, but he was transferred to an infectious diseases unit on October 4. Lumbar puncture on September 30 had shown a cell count of 8/c.mm.; protein 47 mg. and sugar 58 mg./100 ml. Coxsackie B5 virus was isolated from the stool after his transfer to the infectious diseases unit.

Case 12.—A youth of 16 was admitted to Belvidere Hospital on October 4, 1959, within a few hours of the onset of headache and vomiting, which were his only symptoms. He was found to be moderately ill, with nuchal rigidity and Kernigism. C.S.F. cell count was 2/c.mm.; protein 30 mg. and sugar 71 mg./100 ml. Two days after admission he was afebrile and had no complaints. Coxsackie B5 virus was isolated from the stool.

E.C.H.O. Virus Infections

An E.C.H.O. virus was isolated from 74 of the cases: 13 of these viruses belonged to an already known type—namely, four cases of type 6, two cases each of types 3 and 5, and one case each of types 1, 9, 11, 14, and 15. From the remaining 61 patients an E.C.H.O. virus of a previously unidentified type was isolated. This was given the designation "Frater," the name of the child from whom it was first isolated. A further six cases of Frater virus infection were diagnosed serologically (Duncan, 1960b).

The number of cases (13) produced by the known E.C.H.O. types is too small for analysis. One of the two children in category C had a normal cell count and was thought to have tonsillitis. The other (Case 13) was included in this category because bacterial meningitis could not be definitely excluded in view of the history of illness in his sibling.

Case 13.—A boy aged 1 year 4 months was admitted to Ruchill Hospital on December 4, 1959. His illness had an insidious onset in which vomiting was a main feature. C.S.F. showed 175 cells/c.mm. on admission. Protein and sugar were not estimated. E.C.H.O. virus type 11 was excreted in the stool on December 5. A sister was in another hospital with meningitis, but the cell count on admission was "very high." No bacteria were seen, but she was regarded as suffering from bacterial meningitis controlled by chemotherapy given prior to admission.

The 67 Frater virus infections formed the largest single virus group. Serological evidence of infection was obtained from one patient in each of the months March and June, but no isolations were effected until July. Most of the infections were encountered during July to September, with a peak in August. After September the outbreak tailed off rapidly. As with Coxsackie A7, the cases were confined to the Clyde Valley and Dundee areas, mainly involving the former, in which the cases first appeared (Table VI).

TABLE VI.—*Seasonal Incidence of Frater Virus Infections*

Month of Onset	Clyde Valley Area	Dundee District
March	1	0
June	1	0
July	13	0
August	20	4
September	15	4
October	3	3
November	2	0
December	0	1

Reference to Table II shows another striking feature. As with the other infecting agents, male patients predominated, an overall ratio of nearly 3:1 being observed. The Frater virus infections, however, occurred at a later age. Thus only 12 cases were seen in the first 5 years, 20 in the second, and 19 in those from 11 to 14 years. Indeed, just less than one-quarter were over the age of 15 years. This contrast between the age distribution of the Frater virus and the Coxsackie A7 infections is quite striking, and might be regarded as suggesting that this was a newcomer to the Scottish scene.

Category A (1 Case)

Frater virus was associated with a case of paralysis closely resembling poliomyelitis.

Case 14.—A boy aged 1 year 2 months was admitted to Ayrshire Central Hospital on July 27, 1959. He was found to have complete flaccid paralysis involving the left arm. There was slight improvement during the initial period in hospital, but at the time of transfer to an orthopaedic unit

paralysis was still extensive. The child had received two injections of poliovaccine four and five months previously. Sera obtained on the 16th and 29th days of illness showed unchanging titres of 128 to Frater virus and 32 to poliovirus types 2 and 3; antibodies to type 1 poliovirus and Coxsackie A7 virus were undetectable. Frater virus was first isolated from a stool on August 6, 1959.

Category B (62 Cases)

Tables II and III show some of the main features to which reference has already been made in describing the Coxsackie A7 cases. That Frater infections reached hospital a little earlier was not explained by any difference in the mode of onset, which was classified as sudden in a similar proportion in both. Headache and vomiting seemed a more commanding presentation in the Frater infections and pain on eye movement and photophobia occurred more often, but it must be remembered that the Frater infections occurred in an older age-group whose more vocal complaint might cause the practitioner to ask for early hospital admission.

One patient from whom Frater virus was isolated showed a transient paresis in hospital. The following is a brief summary.

Case 15.—A boy aged 13 years was admitted to Belvidere Hospital on August 17, 1959. He complained of headache and anorexia, pain in the muscles of the left thigh, and pain on moving the eyes, for one day before admission. He had difficulty in swallowing on the day of admission. He appeared acutely ill, with pyrexia of 101.4° F. (38.6° C.), and nuchal rigidity and Kernigism were present. Weakness of the arms and the right leg was noted on the evening of admission, but by the following morning this had disappeared. Neck stiffness disappeared after 48 hours, but returned three days later and persisted for four days. Lumbar puncture: 25 lymphocytes/c.mm., protein 12 mg./100 ml., sugar normal. Frater virus was isolated from the stool.

Category C (4 Cases)

Case 16.—A boy aged 5 years was admitted to King's Cross Hospital on August 13, 1959. He had a sudden onset of illness associated with headache, abdominal pain, and diarrhoea. Weakness of the right arm was found to be due to lower motor neurone paralysis of the shoulder-girdle. There was no sensory involvement. The C.S.F. showed: cells 0; protein 30 mg. and sugar 52 mg./100 ml. He was only mildly ill after admission, and paralysis had disappeared after six days in hospital. Frater virus was isolated from the stool.

Case 17.—A girl aged 9 years was admitted to Ruchill Hospital on August 24, 1959. She had been off colour for one day before admission, with headache and vomiting. She was found to have pyrexia, nuchal rigidity, and Kernigism, and was admitted as a probable case of meningitis. C.S.F. cell count was 12/c.mm.; protein and sugar levels were normal. Frater virus was isolated from a stool specimen on August 27. Stools sent for bacteriological examination proved positive for Flexner dysentery. This condition was treated with a sulphonamide, and the patient was discharged well after 12 days.

Case 18.—A girl aged 12 years was admitted to Ruchill Hospital on September 9, 1959, with a recent history of tonsillitis, from which she had recovered sufficiently to return to school. Headache had developed on the day prior to admission, and was accompanied by vomiting and neck pain. On admission there was slight nuchal rigidity and Kernigism, and pyrexia of 101.4° F. (38.6° C.) was found. Pyrexia persisted during the first day in hospital. The tonsils were markedly enlarged, with a purulent exudate, but with penicillin treatment the condition improved rapidly. C.S.F. cell count on admission was 12/c.mm.; protein and sugar levels were normal. White-cell count was 20,300/c.mm., with 84% polymorphonuclear cells. Stool examination showed Frater virus. A mixed growth was cultured from a throat swab.

Case 19.—A girl aged 7 years was admitted to King's Cross Hospital on October 24, 1959. She had had jaundice four weeks earlier, and presented with drowsiness, vomiting, abdominal pain, and headache. No meningeal signs were present, but temperature of 101° F. (38.3° C.) and pulse rate of 115 a minute were recorded. The C.S.F. cell count was 2/c.mm.; protein 35 mg. and sugar 51 mg./100 ml. She settled gradually over the first five days in hospital. The condition was thought to be mainly encephalitic. Frater virus was isolated from the stool. This girl's sister, aged 10 years, had been admitted on October 19 with a history of headache and meningeal signs of eight days' duration. She also had a history of jaundice three weeks prior to admission. Lumbar puncture produced C.S.F. with 195 cells/c.mm., mainly polymorphonuclear; protein 50 mg. and sugar 45 mg./100 ml. Frater virus was isolated from the stool. Progress in hospital was rapid and all meningeal signs disappeared within three days.

Other Infections

During the year 35 patients were seen in whom a possible aetiological agent was identified which was other than one of the three main viruses discussed. Five of them were, however, also infected by viruses belonging to one or other of the main groups as shown: (1) Coxsackie A7 virus and adenovirus type 1 were isolated from the stool (category B). (2) An untyped strain of Coxsackie group B virus was isolated from the stool of a patient in whom leptospirosis was diagnosed serologically (category C). (3) Frater virus was isolated from a patient with a rising titre of antibody to mumps (category B). (4) E.C.H.O. virus type 1 was isolated from a patient with a rising mumps antibody titre (category C). (5) Coxsackie type A7 virus and another virus which remained unidentified were isolated from a patient with serological evidence of leptospirosis (category B).

The 30 other patients in this group included 12 cases of mumps (11 category B, one category C), six cases of leptospirosis (all category B), four cases of adenovirus infection (of which three category B cases were diagnosed serologically and one category A case was identified by isolation of type 7 adenovirus), two cases of herpes meningo-encephalitis (both category B), one case of paralytic poliomyelitis, one of louping ill (category B), and four cases from which virus was isolated but remained unidentified (three category B, one category C).

Category A (2 Cases)

Poliovirus type 1 was isolated from a man aged 28 who was taken ill in the month of July with typical paralytic poliomyelitis affecting the right leg. This was still evident on his transfer to an orthopaedic unit some weeks later. Lumbar puncture was not done in the presence of typical paralytic illness.

The other case occurred in January, 1959, in a female infant of 7 months who became fevered and irritable four days before admission to hospital. Vomiting was a feature of his illness, and his parents reported that he was not moving his right arm. The arm was described as flail-like at the time of admission, but paralysis had almost gone in 10 days; there was slight deltoid weakness on dismissal a week later. C.S.F. cell count was 436/c.mm.; protein 30 mg. and sugar 68 mg./100 ml. Suckling mice were not inoculated in this instance, but adenovirus type 7 was isolated in tissue culture.

Category B (29 Cases)

This category included 12 of the 14 cases of mumps, seven of the eight cases of leptospirosis, four of the cases of adenovirus infection, two cases of herpes infection, three of those in which the virus isolated remained unidentified, and one case of louping ill (McKenzie, to be published).

Mumps.—Of the patients with mumps only four had manifest salivary-gland swelling. The sexes were equally represented and the age range was from 3 to 26 years. Signs of meningeal irritation were minimal in the majority and the illness was mild with rapid recovery. C.S.F. cell counts ranged from 42 to 1,000/c.mm.; protein levels were usually slightly above normal.

Leptospirosis.—The seven patients in this category were aged between 9 and 34 years; four were female. All had obvious meningeal irritation on admission and all made an uneventful recovery. In one there was a history of contact with a sick dog. Headache, vomiting, fever, and listlessness were common symptoms. C.S.F. cell counts ranged from 100 to 1,500/c.mm. with one exception where the count on admission was 2/c.mm. but on the following day was reported as 1,000/c.mm. Protein levels varied from 15 to 120 mg./100 ml.

Adenovirus Infections.—Four of these were seen. One patient—a 5-month-old infant—was infected with adenovirus type 1 and Coxsackie A virus type 7. He had a mild illness from which he made a rapid recovery. The three other cases were identified by serological examination; two had unchanging titres of 256 and 512 respectively and the third showed a rise of titre from <8 to 16. One of these patients—a male child of 14 months—remained ill and febrile for seven days, but the temperature was maintained at normal levels for the subsequent seven days. A further rise occurred then and the presence of a cerebral abscess was suspected. Studies carried out in a neurosurgical unit failed to confirm this diagnosis and he was finally classified as a case of aseptic meningitis. C.S.F. cell count at the time of admission was 218/c.mm. Protein and sugar levels were reported to be normal.

Herpes Infection.—The two patients in this group, a man aged 25 and a woman aged 28, presented as cases of meningo-encephalitis. They have been described in detail elsewhere (Ross and Stevenson, 1961).

Virus Isolated but Not Identified.—The three patients in this group were thought to be cases of lymphocytic meningitis because of the presence of nuchal rigidity and Kernigism and pleocytosis in the C.S.F. All had a history of headache and vomiting, and pyrexia between 100 and 102° F. (37.8 and 38.9° C.) was present for some hours after admission, but the course of illness was uncomplicated.

Louping Ill.—A sheep farmer was admitted to Belvidere Hospital on October 23, 1959, acutely ill with headache and signs of meningeal irritation. Examination of the C.S.F. revealed a lymphocytic meningitis. The history given showed that on September 24 he had destroyed a lamb with convulsions by slitting its throat, getting blood on his hands in so doing. A week later he complained of severe pain in chest and abdomen, and retired to bed, where he was treated for "flu" for seven days. During the next six days, although up and about, he had some facial stiffness and was "not seeing correctly." On October 17 he collapsed, was febrile, had severe headache and vomiting, and complained of pain in the eyes and vertigo. Within 48 hours of admission to hospital the vomiting ceased and his general condition greatly improved. Intermittent headache continued with gradually lessening severity until he was dismissed on November 7. For more than a month after leaving hospital he complained of lack of energy and recurring headaches, although these were not severe. Indeed, it was almost three months before he was completely well. A high and twofold rise in antibody titre for louping ill was obtained by both complement-fixation and haemagglutination-inhibition tests.

Category C (4 Cases)

Two of these cases had serological evidence of mumps, and in one of them E.C.H.O. virus type 1 was isolated from the stool. These children, a girl aged 7 and a boy of 11 years, were siblings, and an older sister was in a general hospital at the time of their admission in May, 1959. She was then thought to have viral meningitis, but the final clinical diagnosis was influenza. There was no parotid enlargement in these cases. Lumbar puncture was performed on the two younger children when the diagnosis of virus meningitis was made in their sister, but by then both had been ill for some eight or nine days. The C.S.F. cell counts were 4 and 0/c.mm., and protein level was 50 mg./100 ml. in both cases. Their illness appeared to be mild tonsillitis; both had pyrexia over 101° F. (38.3° C.) on admission. Recovery was uneventful. Both patients showed rising titres of complement-fixing antibodies to mumps "soluble" antigen.

In the third case leptospirosis was diagnosed in the presence of a febrile illness with meningeal irritation in a boy aged 12 years. Secondary fever from the 17th to the 22nd day of illness, combined with loss of hair, suggested leptospiral infection, and complement-fixation and agglutination tests confirmed this diagnosis. Coxsackie group B virus was found in the stool but was not further identified. C.S.F. examination on admission was normal.

In the fourth case a boy of 4 years had a history and clinical course very suggestive of meningitis, but C.S.F. findings were within normal limits. The virus isolated from his stool unfortunately failed to survive storage and was not identified.

No Infection Identified

In 142 cases infection was not identified, but from 20 of them no specimens were available for virological tests (17 in category B and three in category C). The main features of this group are shown in Tables I to IV. As compared with the main aetiological groups the disproportion between the sexes was not so marked. Only 34 of the 142 patients were under 5 years of age—a proportion similar to that in the Frater and Coxsackie B virus groups. Clinically there were no obvious differences between this group and the others. Although these cases were seen throughout the 12 months, they predominated between May and November, with peaks of incidence in May and June, just before the maximum incidence of Coxsackie A7 infections, and in August, coinciding with the peak of Frater infections.

In assessing reasons for failure to identify an infection in these cases, the possibility of deterioration of specimens during transit from the more distant centres was considered. This did not appear to be the explanation, since the rates of virus isolation were similar and indeed somewhat higher for Dundee, which was the furthest from its diagnostic laboratory.

Category A (3 Cases Tested)

Two were male infants, aged 7 and 10 months, admitted in February and May, both of whom had paralysis involving the left arm that was regarded as typical of poliomyelitis. Weakness of the arm muscles was still evident 12 to 14 months after an illness with meningeal signs and an increased cell count in the C.S.F. Stools specimens and paired sera were examined from both infants with negative results; suckling mice were not used in the investigation of one of them.

The third patient was a woman aged 22 who became ill in June, with headache, anorexia, listlessness, and pain and weakness in the right arm. She had pyrexia up to 102° F. (38.9° C.) for 24 hours in hospital. All muscles of the arm were affected, and weakness was still present a year later. C.S.F. cell count was 80/c.mm., with protein 100 mg. and sugar 49 mg./100 ml. No virus was isolated from stools inoculated in tissue cultures and suckling mice. A single specimen of serum was obtained only several months after the acute illness, and was not tested.

Category B (106 Cases Tested)

This category contained the majority of cases, and consisted of patients whose illness presented as aseptic meningitis but in whom neither the physical signs nor the clinical history was of help in indicating the aetiological agent. Attention has already been drawn to the main features of the group in Tables I to IV where they are compared with those of the Coxsackie A7, Coxsackie B5, and Frater groups.

Category C (13 Cases Tested)

Three patients were seen in whom polyneuritis of Guillain–Barré type was present. These were:

(1) A boy of 18 months, admitted in February, 1959, with a history of headache, fever, and weakness of the right leg, developed quadriplegia. The C.S.F. cell count was 2/c.mm., and protein level 100 mg./100 ml. Improvement was gradual, and he still had weakness of the right leg when transferred to an orthopaedic unit after six weeks. No poliovaccine had been given.

(2) A boy of 4 years became ill in August, 1959, with fever, vomiting, and abdominal pain. The cell count on admission was 2/c.mm., and protein 70 mg./100 ml. The child made a complete recovery from his quadriplegia and was dismissed after five weeks. Injections of poliovaccine had been given in June and July.

(3) A woman aged 29 had a febrile illness from which she made some recovery, but became ill again after 12 days with polyneuritis affecting all four limbs and the muscles of respiration. She made a very slow recovery and was later transferred to an orthopaedic unit. The C.S.F. cell count was 2/c.mm., and protein 170 mg./100 ml.

The remaining 10 cases are summarized as follows:

(4) A man aged 26 was transferred in April, 1959, from another hospital after tracheostomy for respiratory care. There had been a gradual onset of coma, and the presence of a cerebral abscess was suspected, but no confirmation was obtained on ventriculography. His course was a stormy one, with quadriplegia, thrombophlebitis, and staphylococcal septicaemia, but he made a gradual and complete recovery. The condition was thought to be an acute diffuse encephalitis with bulbar paralysis. No C.S.F. examination was carried out. Stool and serum examination yielded no information on possible aetiology.

(5) A girl of 13 years was admitted in January, 1959, with a history of dysphagia, nasal speech and regurgitation, paraesthesiae of the feet, faintness, and dizziness of two days' duration. She was afebrile. Clinically her illness suggested post-diphtheritic palsy involving the right side of the palate, but no confirmation of this was obtained. C.S.F. cell count was 1/c.mm.; protein and sugar levels were within normal range. She was dismissed well after three weeks, showing only slight nasal intonation in her speech.

(6) A girl of 15 years was thought to be a case of encephalitis. On admission her C.S.F. cell count was 2/c.mm. and the protein level 15 mg./100 ml. She had been ill for one day with headache, vomiting, anorexia, and drowsiness when admitted on May 13, 1959. Her speech was slurred, and over the next two or three days her drowsiness increased, but by May 18 she was "fully conscious and alert." E.E.G. examination confirmed the diagnosis of encephalitis. She was discharged well 10 days after admission.

(7) This patient—a woman aged 39—was admitted in December, 1959, with a history of headache, vomiting, fever, and backache. She was pyrexial and nuchal rigidity and Kernigism were present. Headache and neck stiffness persisted for five days. It was considered possible that she had had meningococcal meningitis that had been partially treated before admission, but "the proportion of polymorphonuclear cells in the C.S.F. was not high enough." On admission the cell count was 360/c.mm., protein 130 mg. and sugar 33 mg./100 ml.

(8–13) Six patients were included in this category because, although they presented the clinical picture of meningitis, there was no increase in C.S.F. cell count, and they did not, therefore, meet the diagnostic criteria of the majority of the series. They were admitted between March and November, and their age range was from 4 months to 27 years.

Cerebrospinal Fluid Examinations

Lumbar puncture was carried out in most cases at the time of admission to hospital. In a small number of cases complete details of the examination were not recorded on the form, but estimates of the cell count and protein level were available for patients in the main virus groups as shown in Tables VII and VIII. A count of up to 12 cells in the C.S.F. was regarded as normal. The results in the group of patients in whom no aetiological agent was identified are given for comparison. There is little indication from these results that a particular cellular response or protein level was associated with any individual agent. On the whole neither protein levels nor cell counts were markedly raised.

TABLE VII.—*Cerebrospinal Fluid Examination (Cell Count)*

Cell Count per c.mm.	No. of Cases, Infecting Agent			
	Coxsackie A7	Coxsackie B5	Frater	None
–20	2 (6·1)	3 (26·7)	8 (12·1)	18 (12·8)
–100	11 (33·3)	1	26 (39·4)	52 (36·6)
–200	11 (33·3)	6 (40)	18	32
200+	9	5	14	39
Not recorded	1	—	1	1
Total	34	15	67	142
Highest count	1,390	712	1,920	1,400

Figures in parentheses are the percentages of the recorded totals.

TABLE VIII.—*Cerebrospinal Fluid Examination (Protein Level)*

Protein mg./100 ml.	No. of Cases, Infecting Agent			
	Coxsackie A7	Coxsackie B5	Frater	None
–30	19	9	33	63
–60	6 (78)	2 (73)	22 (83)	46 (78)
–100	7	3	8	28
100+	—	1	3	10
Not recorded	2	—	1	3
Total cases	34	15	67	150

Figures in parentheses are the percentages of the recorded totals.

Poliomyelitis Immunization

Information about 88 patients in the Western Region is analysed in Table IX according to the number of injections and the various aetiological agents. In two-thirds of these patients for whom special inquiry was made, confirmation was obtained that at least one injection had been given against poliomyelitis. Twenty patients were known to have been fully immunized; two of these had an illness in which paralysis featured (Cases 2 and 4, both infected with Coxsackie A7 virus). The clinical categories of the 88 patients were: A, 8; B, 76; and C, 4.

TABLE IX.—*Polio Immunization History—88 Cases of Special Inquiry*

No. of Injections	Coxsackie A		Coxsackie B		E.C.H.O. Virus		Other Infection	No Infection	Total
	Type 7	Other	Type 5	Other	Frater	Other			
0	5	—	2	1	7	—	1	14	30
1	2	—	1	—	—	—	1	3	7
2	6	1	—	1	7	2	4	10	31
3	5	—	—	—	5	2	1	7	20
Total	18	1	3	2	19	4	7	34	88

Discussion

Aseptic meningitis, and virus meningo-encephalitis in general, presents a perennial problem. Sporadic cases occur throughout the year with annual outbreaks in summer and autumn. The number of cases seen in any one hospital may be small, except during large epidemics. The latter, if caused by an agent such as poliovirus which causes a relatively high rate of paralysis, may give rise to public alarm. Sporadic and milder cases may be a source of worry and diagnostic difficulty to the clinician, and laboratory investigations are essential for precise differentiation of the various infections that can give rise to illness of this clinical pattern.

The known causes of the broad syndrome of aseptic meningitis are as follows: (1) enteroviruses (poliovirus, Coxsackie virus, E.C.H.O. virus); (2) mumps; (3) herpes simplex; (4) lymphocytic choriomeningitis (a virus disease of mice, occasionally transmitted to man); (5) arbor viruses (in Scotland, louping ill is the indigenous member of this group); (6) other viruses—for example, measles and herpes zoster; (7) non-viral agents—for example, leptospirae and tubercle bacilli.

By the application of a battery of tests we were able to show the presence of such infections in more than 50% of cases of aseptic meningitis in 1959. Many viruses were associated with only small numbers of illnesses. The most striking phenomena were the almost complete disappearance of poliovirus, the emergence of Coxsackie A7 virus as the main cause of "paralytic poliomyelitis" and of aseptic meningitis during early summer, and the appearance of the previously unrecognized Frater virus as the main cause of aseptic meningitis during the second half of the year.

Coxsackie A7 viruses were isolated from cases of paralytic and fatal illness for the first time in 1952 in Russia: three strains were isolated from pooled specimens from six patients, of whom two died (Chumakov *et al.*, 1956). They were regarded as a fourth type of poliovirus, and seven additional isolations were made from paralytic cases in a later outbreak in the same town of Karaganda (Voroshilova and Chumakov, 1959). Similar single cases were also reported from the U.S.A. (Ranzenhofer *et al.*, 1958) and from Scotland (Grist *et al.*, 1960). The outbreak of 1959 in Scotland is thus the largest yet recorded. As it occurred in a year when polioviruses were virtually absent from the community, the epidemiological circumstances were particularly favourable for proving that the associations of Coxsackie A7 infection with paralytic illnesses were causal. Inoculation of suckling mice with every stool extract prepared in the Glasgow laboratory in the two months June and July provided additional evidence of "guilt by association": Coxsackie A7 viruses were isolated from five of six cases of "paralytic poliomyelitis," from 18 of 57 cases of non-paralytic non-bacterial meningitis (other enteroviruses were isolated from 19 of the 39 cases from whom Coxsackie A7 viruses were not isolated), and from only one (Case 8) of 60 cases of other types of illness (diarrhoea in children, acute respiratory illnesses, etc.). That this infection was not new to the community was suggested by the age distribution of cases (70% of pre-school age) and by the presence of detectable antibodies in 46% of blood-donor sera collected the year before the outbreak (Grist, to be published). It is important to note that Coxsackie A7 virus can cause paralytic and fatal illnesses, clinically indistinguishable from poliovirus infection, in persons immunized with poliovaccine; and that in order to detect this virus it is necessary to inoculate suckling rodents, monkeys, or perhaps adult cotton-rats (Voroshilova and Chumakov, 1959).

Of the recognized 28 types of E.C.H.O. virus, types 4, 6, and 9 have been reported as causing epidemics of aseptic meningitis. Until the appearance of Frater virus, which has the characteristics of a previously unknown E.C.H.O. virus, only type 9 E.C.H.O. virus was known to have caused such epidemics in Britain. The involvement of higher age-groups in the Scottish outbreak of Frater infection in 1959 suggested that this virus was relatively new to the community—a suggestion supported by the absence of detectable antibodies from all but 9% of the blood-donor sera collected in 1958; on the other hand, antibodies to Frater virus were found in several batches of gamma-globulin prepared in Scotland during the previous eight years (Duncan, 1961). It is notable that this virus was detected relatively poorly by the usual monkey-kidney-tissue culture used for isolation of enteroviruses, and was best isolated in human thyroid or human amnion cultures (Duncan, 1960b). Aseptic meningitis was the illness most commonly associated with Frater virus infection; but that this virus can occasionally cause more serious disease is suggested by the paralysis of one and transient paresis of a second case infected by it.

Of the other viruses isolated, that most frequently encountered was Coxsackie B5 virus, a well-recognized cause of aseptic meningitis. The diagnostic value of routine serological tests was shown by the detection of mumps in 4.2% and leptospirosis in 2.3% of cases of aseptic meningitis. Although louping ill is endemic among sheep in Scotland only one human case of this arthropod-borne infection was detected. Previous studies had similarly failed to show evidence of louping-ill infection among cases of paralysis or encephalitis in Scotland in 1956 and 1957 (Grist *et al.*, 1960). The situation apparently differs from that in Northern Ireland, where serological evidence of louping ill was found in cases resembling paralytic poliomyelitis (Likar and Dane, 1958).

After completion of all tests, the cause of a proportion of these illnesses remained undiagnosed. To some extent this must reflect inadequacies of technique: only single specimens of stool were examined from each patient, and most of these had remained at atmospheric temperature for a day, or occasionally longer, during postal transmission. The methods of virus isolation were comprehensive, but it is notable that, of the two most prevalent viruses, one was best detected by human-thyroid-tissue cultures which are not in general use, and the other was undetectable by standard tissue-culture methods and was revealed only by inoculation of suckling mice. It seems likely that other relevant viruses await discovery by techniques not yet tried.

It is not many years since poliovirus infection changed from being the cause of sporadic infantile paralysis to producing epidemics of paralytic poliomyelitis affecting older persons. Serological evidence suggests that Coxsackie A7 virus has previously been endemic in the population of Western Scotland, but in 1959 it caused a significant outbreak with cases of paralysis and death. Perhaps the emergence of such "new" virus diseases reflects a disturbance of the long-established ecological balance, possibly resulting from improved living conditions and socio-economic standards of the population. Further study is required to show whether Frater virus is a "new" virus or an antigenic variant of an "old" one, but it seems likely that enteroviruses, like influenza viruses, are subject to selection pressure favouring the spread of new antigenic variants; and indeed antigenic variants of several E.C.H.O. viruses have already been encountered in nature (Karzon *et al.*, 1959). The virtual disappearance of poliovirus in Scotland since 1958 may simply represent the trough in the natural cycle of varying prevalence of this enterovirus, yet its coincidence with widespread use of Salk-type poliovaccine raises the question whether this may have played a part by preventing viraemia and thus suppressing secondary pharyngeal invasion of poliovirus. In any case, reduction of the number of paralytic poliovirus infections as a result of polio vaccination should throw into greater prominence cases of paralysis due to such other viruses as Coxsackie type A7.

Summary

The epidemic pattern of paralytic and non-paralytic poliomyelitis-like illnesses seen in three hospital regions in Scotland in 1959 is described. The majority of the 310 patients were without paralysis but showed changes in the cerebrospinal fluid; three categories are used to describe the clinical features.

Virological examinations were carried out in all but 20 cases, and 174 infections were identified in 168 individuals. The viruses responsible for the majority of identified infections were in order of frequency: Frater, Coxsackie A7, and Coxsackie B5. Infections seen in smaller numbers were due to E.C.H.O. (types 1, 3, 5, 6, 9, 11, 14, and 15), Coxsackie (group A type 9 and untyped; group B type 2), mumps, adenovirus, herpes, poliovirus (1 case), and louping ill (1 case). Leptospiral infections are also included in the series.

There was evidence of epidemic grouping of cases of Coxsackie A7 and Frater infection. Paralysis was associated with both these viruses; one child infected with Coxsackie A7 virus died after a brief paralytic illness.

The majority of patients were children; males predominated; the age distribution was not uniform within the different aetiological groups. These groups were examined with regard to onset, month of onset, and C.S.F. results. Summaries are presented of cases of particular interest.

We thank our medical and technical colleagues in the wards and laboratories of individual hospitals, the many practitioners and medical officers of health who helped us in our inquiries, and Dr. J. S. Porterfield, of the National Institute for Medical Research, Mill Hill, London, for the haemagglutination-inhibition test for louping ill.

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INCIDENCE OF POST-OPERATIVE PNEUMOPERITONEUM AND ITS SIGNIFICANCE*

BY

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Although there is no lack of information about radiological appearances in the chest after abdominal surgery, and much has been written concerning post-operative pulmonary complications, little attention has been drawn to appearances below the diaphragm. Bannen (1944) suggested that pneumoperitoneum is always present in the closed abdomen after every abdominal operation, that it is always bilateral, but that it is transient and absorbed within seven days. Keiser and Lemmertz (1947) recorded the incidence and duration of post-operative air in four groups of abdominal operations as shown in Table I.

TABLE I

Operation	No. of Cases	Air Present	Average Duration
Appendicectomy	35	27	3·3 days
Gastrectomy	18	18	7·6 ,,
Cholecystectomy	10	10	4·9 ,,
Colon resections ..	5	5	9·8 ,,

Sergievskiy (1947) studied 105 cases and found that the absorption of air took three to nine days, according to the amount present, and that, rarely, it remained for as long as two to four weeks or more; the amount of air was found to be related to the site of incision in relation to the diaphragm, more being retained in upper abdominal operations. Harrison *et al.* (1957) analysed 104 cases and confirmed a higher incidence for upper

*Abridged and adapted from a thesis accepted for the Mastership of Surgery, University of Birmingham.

abdominal incisions, with the duration proportional to the volume. Their results are shown in Table II. They included in their paper Gerwig's series of 37 appendicectomies in which 25 showed post-operative air lasting an average of three days; in 80% the air was absorbed within four days.

TABLE II

Operation	No. of Cases	Air Present	Average Duration
Inguinal hernia	32	1	1 day
Appendicectomy	15	4	2·5 days
Cholecystectomy	9	8	3·4 ,,
Gastrectomy	16	14	6·1 ,,
Colon resections	13	10	3·8 ,,
Other laparotomies	9	5	2 ,,
Ventral and epigastric hernias	5	2	6 ,,
Aortic and iliac arterial operations	3	2	4 ,,
Miscellaneous	19	9	3·5 ,,

Present Series

In order to discover the incidence, distribution, and duration of post-operative pneumoperitoneum, serial radiographs were taken in a consecutive number of general surgical cases. In all, 82 patients have been studied: the operations are listed in Table III.

TABLE III.—82 *Patients Undergoing Abdominal Operations Studied by Serial Post-operative X-ray Films*

Group	Operation	No. of Cases
A. Gastric operations (47)	Gastrectomy	41
	Gastroenterostomy	2
	Pylorectomy	2
	Revision gastrectomy	1
	Abdominal vagotomy	1
B. Other upper abdominal operations (6)	Upper laparotomy	1
	Cholecystectomy	4
	Splenectomy	1
C. Lower abdominal operations (23)	Lower laparotomy	2
	Appendicectomy:	
	Paramedian with laparotomy	13
	McBurney muscle-splitting incision	1
	Incisional hernia	2
	Inguinal ,,	1
	Colectomy	3
	Ileo-colostomy	1
D. Pelvic operations (6)	Anterior resection of colon	1
	Abdomino-perineal resection	2
	Ovarian cystectomy	1
	Ovariectomy	1
	Hysterectomy	1

Each patient was radiographed in the upright position within the first three days of operation, and again at intervals until all air had disappeared from the abdomen. Towards the end of the series it was found that the initial film of greatest value was that taken on the second post-operative day; this sometimes showed more air than on the first day, indicating that the air in the peritoneal cavity must take 24 hours or more to become fully distributed under the diaphragm. It was also found that a lateral film is of greater value than an antero-posterior, as air shown on the former is sometimes not seen on the latter.

Results

In the whole series air was not shown in 19 cases but was present to a greater or lesser extent in 63 (76.8%). The amount present was allocated to one of four grades—trace, small amount, moderate amount, considerable amount. The numbers showing air present, in each grade, for the whole series are shown in Table II. The result shown in Table IV compares closely with that of Pendergrass and Kirk (1929), who found that free air was present after 60% of abdominal operations.

TABLE IV.—*Incidence of Post-operative Pneumoperitoneum (82 Cases)*

No air present	19 cases
Grade 1. Trace	11 ,,
,, 2. Small amount	17 ,,
,, 3. Moderate ,,	26 ,,
,, 4. Considerable ,,	9 ,,

It was surprising to find how often a large pneumoperitoneum was unwittingly left, and it appeared that this was apt to happen after many different types of operation. Fig. 1 shows a patient the day after a Polya gastrectomy, with a large right-sided pneumoperitoneum. A large amount of bilateral air present the day after a paramedian appendicectomy is shown in Fig. 2. These were both graded as "considerable" (grade 4 pneumoperitoneum).

Sex and Age.—The sex distribution of the whole series was 52 males to 30 females. The sex incidence was calculated in relationship to occurrence of air. In the lower two grades of pneumoperitoneum the sex distribution was even, but in the two higher grades there were more males than females. Of the 26 subjects with grade 3 pneumoperitoneum, 18 were male and 8 female; with grade 4, eight were male and only one was female. Thus the larger volumes of air tend to be left far more often in males. There seemed to be no relation between age and post-operative pneumoperitoneum. The full age range was encountered in each grade.

Distribution

Attention was next directed to the distribution of air left in the peritoneal cavity. Air that is free in the greater sac rises rapidly to the subphrenic spaces; this is due partly to the fact that the patient always assumes an erect (sitting) position within a few hours of operation, and partly to the pressure gradient within the peritoneal cavity.

The pressure in the general peritoneal cavity is positive (above atmospheric); the pressure in the subphrenic spaces is negative (sub-atmospheric) and approximates to the pressure about the diaphragm—that is, the intrapleural pressure. These observations have been confirmed in animals and in humans by many authors (Overholt, 1930; Salkin, 1934; Banyai, 1946, 1955; Harley, 1955). Thus the subphrenic space is a functional part of the intrapleural mechanism rather than part of the peritoneal cavity. Therefore air introduced anywhere in the peritoneal cavity follows this pressure gradient and rises under the diaphragm, where the pressure is negative as compared with the remainder of the peritoneal cavity. Owing to the pressure gradient, air collects under the diaphragm even if the patient is not in an erect position. The following case is a good example of the movement of air in the peritoneal cavity.

A woman of 63 underwent a recto-sigmoidectomy by the peranal route for prolapse of the rectum. Four days after the operation she developed sudden abdominal pain and distension. *X*-ray examination showed that the anastomosis had leaked and a large amount of air had collected under the diaphragm. The air was released and a temporary colostomy performed; the patient made an uneventful recovery.

This subphrenic air may be bilateral or entirely or predominantly under one dome of the diaphragm. Pendergrass and Kirk (1929) found the right side to be more frequently the location of free gas in the abdomen. The distribution for each case in the present series has been noted and results are presented in Table V. From this it can be seen that in most cases air is present on

the right; in 39 out of 63 cases the air was entirely or mainly in the right subphrenic space. This is explained by the fact that in most laparotomies the liver is separated from the under surface of the left dome of the diaphragm, often by the exploring hand, and being the heaviest of the upper abdominal viscera it falls away, leaving a large air space between it and the anterior part of the diaphragm which persists even when the abdomen is being sutured. This distribution of pneumoperitoneum is subsequently correlated with the distribution of pulmonary complications (Bevan, 1961).

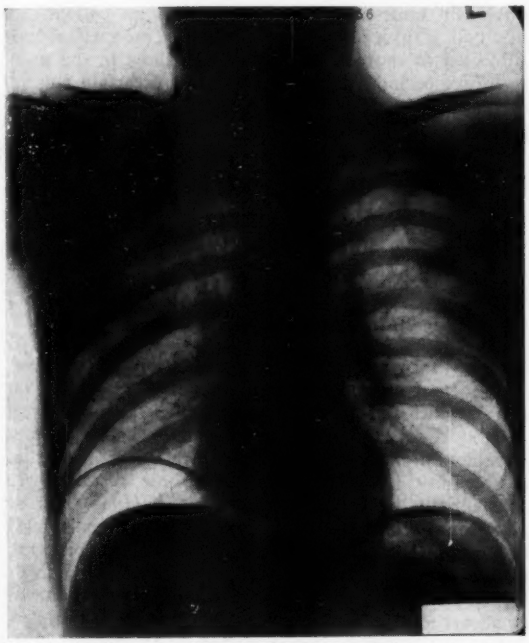

FIG. 1.—Radiograph taken the day after a Polya gastrectomy, showing a large right-sided pneumoperitoneum.

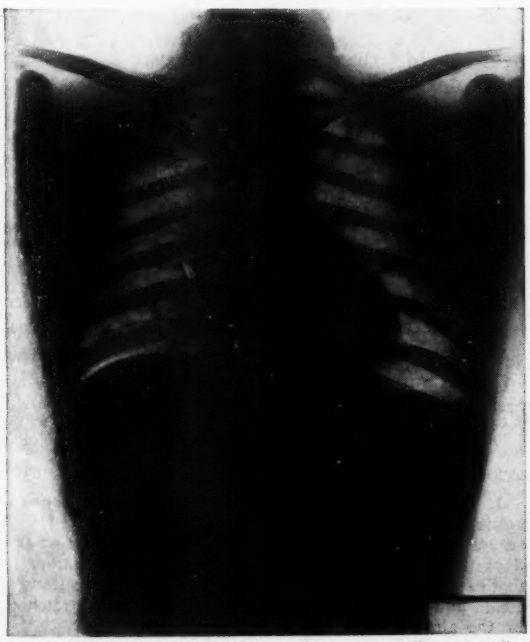

FIG. 2.—Radiograph taken the day after a paramedian appendicectomy, showing a considerable amount of air under both sides of the diaphragm.

It was observed on occasion that a pneumoperitoneum initially unilateral subsequently showed a more bilateral pattern. Fig. 3 shows the same patient as in Fig. 1 four days after operation; the air which was mainly on the right in the first radiograph has become evenly distributed on the two sides in the second. This redistribution, resulting in the bilateral dispersal of pneumoperitoneum, is effected by changes in posture on the part of the patient (Truelove and Lumsden, 1955), such as lying down and turning over at night. Patients who remain propped up and relatively immobile preserve a unilateral pneumoperitoneum. Certain operative procedures also affect the distribution of the air—for example, the common habit of dividing the falciform ligament in doing a gastrectomy facilitates even distribution under both domes of the diaphragm of any air remaining in the upper abdomen. The falciform ligament is the structure mainly responsible for maintaining a unilateral pneumoperitoneum.

TABLE V.—*Distribution of Subphrenic Air in the 63 Cases which Showed Air Present*

Pneumoperitoneum	Right	Left	Bilateral
Grade 1	5	2	4
,, 2	11	2	4
,, 3	18	5	3
,, 4	5	0	4
Total ..	39	9	15

Unilateral air is more likely to lead to certain complications than when more widely dispersed; being localized, its influence is presumably more powerful. The formation of a subphrenic abscess, basal pulmonary collapse associated with air under the same side of the diaphragm, and dehiscence of an abdominal wound are

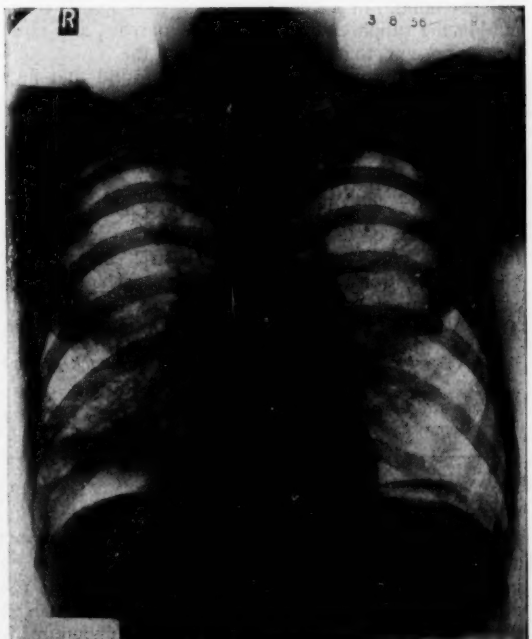

FIG. 3.—Radiograph of the same case as shown in Fig. 1, taken four days after operation; the air has now become evenly distributed on the two sides.

all post-operative complications in which pneumoperitoneum may be a predisposing factor. To avoid these complications, measures leading to the bilateral distribution of the air are to be encouraged, and in this respect free mobility of the patient in the early post-operative period is important.

Absolute Amounts

Estimates of the absolute amount of air present are difficult in the human. As pneumoperitoneum seems to be associated with various complications, it was deemed not justified to introduce measured amounts of air into the peritoneal cavity at the end of laparotomy in order to study the subsequent radiological appearances. The absolute amount of air corresponding to the radiological appearances in the series has been estimated in three ways: (1) by examining radiographs of patients who have undergone therapeutic pneumoperitoneum for tuberculosis, where the amount of air instilled is known; (2) by examining the appearances on radiographs of the small amounts of air introduced during tubal insufflation (Bevan, 1960); and (3) by measuring the volume of air aspirated from the peritoneal cavity at the end of laparotomy (Bevan, 1961). The estimated volumes represented by each grade are given in Table VI.

TABLE VI.—*Absolute Amounts of Each Grade of Pneumoperitoneum*

Grade 1	Up to 100 ml.
,, 2	100–500 ,,
,, 3	500–1,000 ,,
,, 4	1 litre or over

Various factors influence the amount appearing on the radiograph. The time factor is important, as more air may show on the second day than on the first. The patient's build also affects the radiological appearance; in a person of slight or thin build a certain volume of air appears as a much wider zone than in those of broader build. In a thick-set patient with a wide costal margin the subphrenic zone of air is narrow, and more air is present than is suggested on the radiograph. As a very approximate guide, it was found that in a patient of average build a layer of air under the diaphragm ½ in. (1.3 cm.) thick represents about 0.5 litre and a layer 1 in. (2.5 cm.) thick about 1 litre.

Surgical Groups

The series of 82 patients falls conveniently into four main groups of operation—gastric, other upper abdominal, lower abdominal, and pelvic. The incidence of pneumoperitoneum in each group is shown in Table VII. It can be seen that a moderate or considerable pneumoperitoneum was present post-operatively in half the patients undergoing gastric operations (24 out of 47, or 51%), a much higher percentage than in the other groups. The higher grades of pneumoperitoneum occurred in only 17% of upper abdominal, in 35% of lower abdominal, and in 33% of pelvic operations. The lower grades of pneumoperitoneum (trace or small amount) up to 0.5 litre were equally represented among the four groups.

TABLE VII.—*Incidence of Pneumoperitoneum in Each Operative Group*

Group	Pneumoperitoneum					
	None	Grade 1	Grade 2	Grade 3	Grade 4	Total
A. Gastric	11	4	8	20	4	47
B. Upper abdominal	2	2	1	0	1	6
C. Lower ,, ..	5	3	7	6	2	23
D. Pelvic	1	2	1	0	2	6

Duration

The duration of the post-operative air was studied by taking repeated radiographs in the same patient until the air had almost or completely absorbed. It was obviously undesirable to expose any one patient too often to *x* rays, and to avoid any risk no patient was subjected to more than four sets of films in the post-operative period. The exact time that a certain volume of air takes to absorb has been deduced from a composite picture of all these *x*-ray results.

A small pneumoperitoneum (100 to 500 ml.) persists for about one week before it is fully absorbed. On an average a moderate pneumoperitoneum (500 to 1,000 ml.) lasts for 10 days before absorption is complete. In one patient with a pneumoperitoneum of this order air was still present under the diaphragm 15 days after operation. Fox (1948) showed that a pneumoperitoneum of 800 ml. may take two and a half weeks to absorb. A considerable amount of air (1 litre or over) persists for up to two weeks before absorption is complete. In a further case air in some quantity was present on the sixteenth post-operative day, and a trace remained on the twenty-third day; this patient had shown a pneumoperitoneum of over a litre after a partial gastrectomy for a peptic ulcer. These results agree substantially with those of Sergievskiy (1947) and of Harrison *et al.* (1957), but challenge Bannen's 1944 statement that post-operative air is always bilateral, transient, and absorbed within seven days; Spalding's (1946) assertion that post-operative pneumoperitoneum is absorbed "in a day or so" is a manifest understatement. Howkins (1948) quoted an example of post-operative air taking one month to disappear.

Diagnosis

In the immediate post-operative period two other conditions may lead to free air under the diaphragm—subphrenic abscess and an air leak from the lumen of the gut, as caused by a burst duodenal stump or a leaking anastomosis after gastrectomy. Both these conditions must be diagnosed on clinical grounds alone; during the first two weeks after operation a straight radiograph is of little help, for pneumoperitoneum may be present and mimic both these more serious conditions.

Applications

Air in the peritoneal cavity is drawn up into the subphrenic space and held there by negative pressure. In small amounts it probably has little effect after abdominal surgery. However, the larger amounts of post-operative pneumoperitoneum, such as are left in about half the cases of partial gastrectomy, are probably associated with definite post-operative complications.

1. *Post-operative Pain.*—In three cases in this series a grade 4 unilateral pneumoperitoneum was associated with severe pleuritic pain in the same shoulder for the first few days after operation. The pain was similar in nature to that experienced on sitting up after tubal insufflation (Bevan, 1960), and was presumably due to diaphragmatic stretching by the air below.

2. *Basal Pulmonary Collapse.*—Just as therapeutic pneumoperitoneum leads to collapse of a tuberculous lung, so post-

operative pneumoperitoneum may cause basal collapse of the lung. This has been made the subject of a separate study (Bevan, 1961).

3. *Dehiscence.*—An abdomen containing air is more liable to dehiscence of a surgical incision. Distension of the abdomen exaggerates the pressure responses of activities such as coughing and vomiting (Drye, 1948), and in this way intraperitoneal air may lead to dehiscence.

4. *Subphrenic Abscess.*—Pneumoperitoneum encourages the spread of intra-abdominal infection by opening up the subphrenic space (Harley, 1955), and thus, with the patient erect, subhepatic infection is aspirated into the suprahepatic space (Spalding, 1946).

5. *Phlebothrombosis and Pulmonary Embolism.*—It has been shown by rabbit experiments that pneumoperitoneum increases the pressure in the veins of the leg (Bevan, 1958). Venous return along the inferior vena cava is facilitated by the negative intrathoracic pressure cranially and the positive abdominal pressure caudally. This "abdomino-thoracic pump" is impeded by a subphrenic pneumoperitoneum which leads to increased pressure and stasis in the deep veins of the pelvis and legs. In this series there were three examples of thrombo-embolism—two associated with grade 2 and one with a grade 3 pneumoperitoneum.

6. *Delayed Restoration in Gastro-intestinal Function.*—In the group of gastric operations, the average post-operative day of withdrawal of Ryle's tube was 5.0 in those cases with considerable pneumoperitoneum, and 2.6 in cases with no pneumoperitoneum. (In all cases Ryle's tube was used routinely, being removed as soon as the oral intake exceeded the aspirates.) In the whole series the mean post-operative day on which the first bowel action occurred was 4.67 in the group of nine grade 4 pneumoperitoneums, and 4.25 in the group of cases with no pneumoperitoneum. Post-operative pneumoperitoneum appears to be associated with marked delay in gastric emptying after partial gastrectomy and slight delay in return of bowel function.

Summary

Serial radiographs have shown that air occurs in the peritoneal cavity in 76.8% of cases in a series of abdominal operations. The incidence of the larger amounts of pneumoperitoneum is higher after partial gastrectomy than in the other surgical groups—upper and lower abdominal and pelvic operations. The distribution, amounts, and duration of post-operative pneumoperitoneum are discussed.

It is suggested that residual air in the peritoneal cavity may be associated with various post-operative complications.

I am indebted to Professor F. A. R. Stammers for his help and encouragement; most of the patients studied were under his care. I owe much to the other members of the Surgical Unit at the Queen Elizabeth Hospital for helpful discussion and criticism, and I thank the anaesthetists involved for the help they gave. I also thank Dr. K. W. Cross for reading the manuscript, and Mrs. M. K. Mason for secretarial assistance.

The work owes much to the help and co-operation of Dr. O. E. Smith and his colleagues in the radiological department.

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POST-OPERATIVE PNEUMOPERITONEUM AND PULMONARY COLLAPSE

BY

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Many authors have recorded the particular proneness of patients undergoing abdominal operations to develop post-operative chest complications (Elwyn, 1922; Featherstone, 1925; Patey, 1930; King, 1933; Anscombe, 1957—to mention only a few of the larger series). The general conclusions are that pulmonary collapse and consolidation is far commoner after upper than lower abdominal operations, and much more frequent after abdominal than non-abdominal surgery. It is of interest that the incidence shows little reduction over the last five decades, despite all the modern emphasis on the improvement of post-operative respiratory capacity and the prevention of complications. Obviously there are still factors operating to-day that we do not fully understand and cannot completely control. In this connexion the advent of relaxant anaesthesia has not been an unmixed blessing, and is probably associated with a higher rate of post-operative chest complications than the inhalation type of anaesthesia it has replaced.

Many terms have been used to indicate the same pathological process: "post-operative pneumonia," "basal congestion," "mucous bronchitis," "massive atelectasis," and so on, but the pathological picture is in all cases the same as that designated here—collapse and consolidation. Collapse develops in the basal lung fields between the second and the fourth post-operative days owing to a combination of mucus-plugging of the bronchi and weakening of the respiratory effort, and this may become secondarily infected to form a frank pneumonia unless the initiating collapse is resolved in time.

Series A

In a series of 82 patients undergoing abdominal operation, where serial radiographs had been taken after each operation to show the incidence, distribution, and duration of post-operative pneumoperitoneum (Bevan, 1961), radiographs were also taken to demonstrate any pulmonary complications. These complications were graded as mild or major: the mild group comprised peripheral atelectasis, incomplete aeration, or sublobular collapse; and major complications took the form of lobar or segmental collapse or large areas of consolidation; frequently major collapse was associated with consolidation. The incidence of these complications for the 82 cases in the series is shown in Table I, together with the distribution—mainly or entirely right- or left-sided or bilateral.

These cases were completely unselected, and represent the average run of general surgical cases of more than one unit. The rate of pulmonary complications seems disturbingly high: 43 out of 82 cases (52%) showed post-operative radiological changes, and 29 (35%) of these comprised major lobar or segmental collapse, usually with consolidation. The main reason for this high incidence is that all patients were studied by routine post-operative radiographs: clinically the majority showed a pyrexia and a productive cough for a few days and settled quickly with conservative treatment. In the ordinary way they would have been dismissed as being "a bit chesty," and most would not have been radiographed. However, the routine use of radiographs revealed the true state of affairs.

The sex distribution of the 29 cases of major pulmonary complications was found to be 22 male to 7 female. As the distribution for the whole series was 52 male to 30 female, pulmonary complications seem to be commoner in the male, a factor agreed on by many authors (Holmes, 1956; Anscombe, 1957). The major pulmonary complications were also found to vary with age, in that the incidence shows a moderate rise in the higher age-groups.

Another point of great interest is the distribution of the changes. Of the 29 cases presenting major collapse and consolidation, the changes occurred on the right side in 19, mainly at the right base, with some in the right middle lobe and some in both lobes. This distribution does not hold in the group showing mild changes, where there is a more even pattern between the two sides (Table I).

It has been shown that post-operative pneumoperitoneum when it occurs is mainly right-sided (Bevan, 1961). In this series 52 cases showed pneumoperitoneum of some degree, and of these the air was entirely or predominantly on the right in 34 (65%). Thus it would seem that there is some association between the distribution of air and the occurrence of pulmonary complications. In an attempt to follow this correlation further, Table II has been drawn up showing pneumoperitoneum in the vertical columns and pulmonary changes in the horizontal columns. The area outlined by an interrupted line shows the large number of cases in which air is present accompanied by marked pulmonary changes. It can be seen that most of the patients with no air or a mere trace showed no pulmonary changes.

TABLE I.—*Pulmonary Complications in Series A (82 Cases) Showing Incidence and Distribution*

Pulmonary Complications	Total	Right-sided	Left-sided	Bilateral
None	39			
Mild	14	6	5	3
Major	29	19	5	5

TABLE II.—*Correlation Between Post-operative Air and Pulmonary Complications*

Pneumoperitoneum	Pulmonary Complications		
	None	Mild	Major
None	11	5	3
Grade 1	10	1	0
,, 2	8	3	6
,, 3	7	4	15
,, 4	3	1	5
Total	39	14	29

For explanation of enclosed area see text.

It is obviously important to discover if these pulmonary complications were related to any particular group of abdominal operations. The 82 cases can be divided into four main groups of operations: gastric, upper abdominal, lower abdominal, and pelvic. Each of the four groups has been analysed separately to show any correlation between the incidence of post-operative air and the occurrence of pulmonary complications. In Table III the pulmonary changes in each group are shown associated with each grade of pneumoperitoneum (cf. Bevan, 1961). The highest incidence of air is in group A (gastric operations), in which 32 out of 47 cases

TABLE III.—*Group Analysis Comparing Post-operative Air and Pulmonary Complications*

Group	Pneumo-peritoneum	Pulmonary Complications		
		None	Mild	Major
A. Gastric (47)	None	5	4	2
	Grade 1	3	1	0
	,, 2	2	1	5
	,, 3	4	3	13
	,, 4	1	0	3
B. Upper abdominal (6)	None	2	0	0
	Grade 1	2	0	0
	,, 2	0	0	1
	,, 3	0	0	0
	,, 4	0	0	1
C. Lower abdominal (23)	None	3	1	1
	Grade 1	3	0	0
	,, 2	5	2	0
	,, 3	3	1	2
	,, 4	2	0	0
D. Pelvic (6)	None	1	0	0
	Grade 1	2	0	0
	,, 2	1	0	0
	,, 3	0	0	0
	,, 4	0	1	1

For explanation of enclosed area see text.

(68%) show pneumoperitoneum of grade 2, 3, or 4. One-third of group B cases and half the group D cases demonstrated air after operation, but the numbers in these groups are too small to do more than suggest tendencies.

It is apparent that the association between post-operative air and pulmonary complications is most pronounced in the group of gastric operations, and this area of Table III is outlined by an interrupted line. There is also a suggestive correlation of distribution in Table I. Fig. 1 is an example of major collapse and consolidation on the right associated with right-sided pneumoperitoneum. Fig. 2 demonstrates bilateral basal collapse-consolidation with bilateral air. Major collapse at the right base associated with bilateral air is shown in Fig. 3. All these examples followed gastrectomy.

Series B

With a definite correlation established between post-operative pneumoperitoneum and pulmonary collapse, the next problem was to investigate whether it is possible to close the abdomen without leaving residual air and if this would reduce the rate of post-operative chest complications.

A series of studies were made in 37 cases (Series B) on the operating-table while the incision was being closed at the end of an abdominal operation. As the majority of cases showing post-operative air in Series A were gastric operations, gastrectomies were chosen as the main group in this series. There was no other selection; successive cases were taken within a certain time period and some non-gastric operations included. Most of these operations were performed by me, and in all of them the studies were made and the incision was closed

personally. Relaxant anaesthesia was used throughout. Every patient was radiographed within the first three days of operation to show any subdiaphragmatic air and any pulmonary complications. The operations included in Series B are shown in Table IV, and are, of course, quite distinct from the cases in Series A.

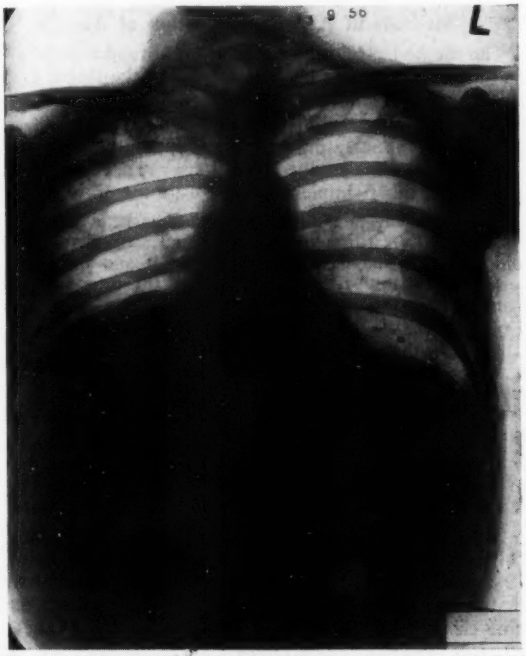

FIG. 1.—Collapse and consolidation at the right base associated with right-sided pneumoperitoneum after partial gastrectomy.

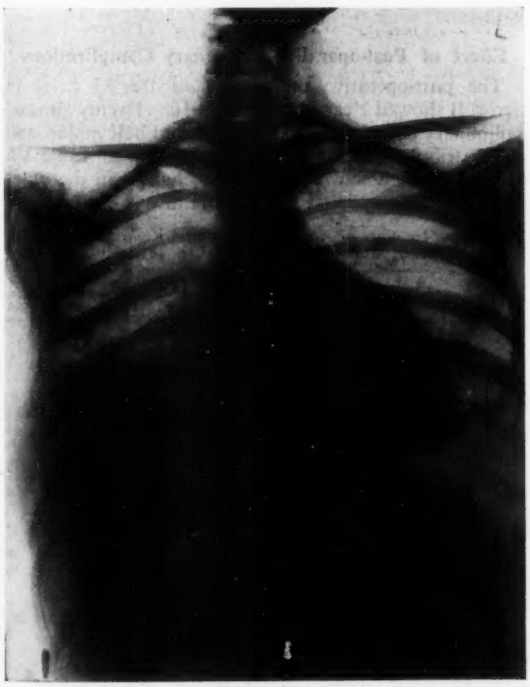

FIG. 2.—Bilateral basal collapse and consolidation with bilateral pneumoperitoneum after partial gastrectomy.

The data obtained from these studies fall under four headings: (*a*) anatomical observations showing how air is left after closure; (*b*) amounts of air remaining at closure and the resulting pressure, as shown by aspiration; (*c*) methods of closing the incision without leaving air, and the effectiveness of these methods; and (*d*) effect of avoiding post-operative pneumoperitoneum on pulmonary complications.

TABLE IV.—*Series B: Operations Subjected to On-table Air Studies*

Gastric operations (29)	Partial gastrectomies	20
	Gastrectomies with vagotomy	2
	Revision gastrectomy	3
	Gastro-enterostomy	1
	,, with vagotomy	1
	Local excision of gastric lesion	1
	Pylorectomy	1
Non-gastric operations (8)	Cholecystectomy	1
	Cholecystectomy with exploration and drainage of C.B.D.	2
	Paramedian appendicectomy	4
	Anterior resection of sigmoid carcinoma	1

Anatomical Observations

As soon as the peritoneum is divided air enters the peritoneal cavity and it becomes a real instead of potential space. When an upper abdominal incision is completed the liver falls away from the diaphragm in a caudal and dorsal direction. This movement is greater if the abdominal musculature is completely relaxed, as with relaxant anaesthesia. Other factors increasing this falling away of the liver from the diaphragm are the exploring hand of the surgeon palpating the upper surface of the liver and the build of the patient, the liver falling further in those whose trunk is long and physique spare. Every abdominal surgeon is familiar with the appearance, in a tall thin patient completely relaxed at the start of a laparotomy, of the liver and upper abdominal viscera lying at the bottom of the abdominal "well" far from the anterior abdominal wall.

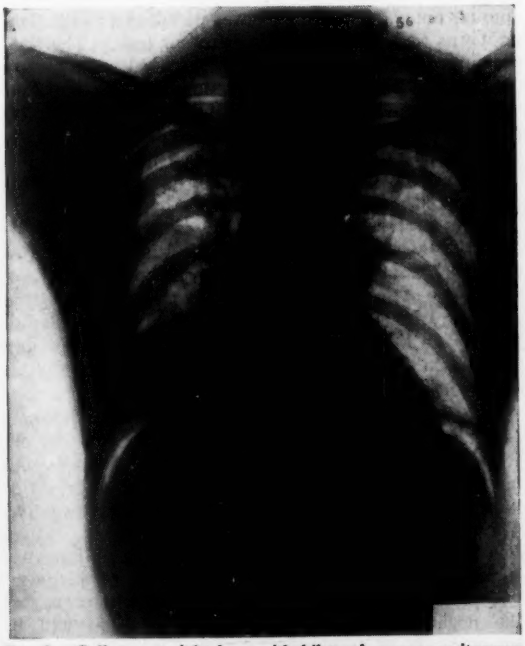

FIG. 3.—Collapse at right base with bilateral pneumoperitoneum after partial gastrectomy.

This relative position of the liver is of fundamental importance with regard to retained air. A space is formed between the liver, diaphragm, and anterior abdominal wall; with the patient in the horizontal position this space has a rigid roof formed by the lower part of the thoracic cage. If the incision is closed with these conditions persisting, a large amount of air will inevitably be left in this space. This volume will be increased by the common practice of the surgeon or his assistant of pulling up the peritoneum as it is closed with a continuous suture, and causing tenting. To avoid the retention of air these considerations must be borne in mind and the conditions reversed. The methods employed are discussed below.

Large amounts of air may be retained after pelvic operations, for similar conditions obtain. Although nowadays the full Trendelenburg position is seldom used (Inglis and Brooke, 1956), most pelvic operations are performed with some degree of head-down tilt. The intestines are packed upwards, and the pelvis, with its rigid walls, is visualized as a complete space. If closure is carried out under these conditions a large volume of air will remain in this "dead space" and will move up under the diaphragm when the patient assumes an upright position.

Aspiration Studies

In 27 of the 37 cases in Series B a large-bore whistle-tip catheter was introduced into the wound and its tip placed under the right dome of the diaphragm. The peritoneum was closed around the catheter with a continuous suture, and the catheter was left issuing from the lower end of the incision. Before the final knot was tied in the continuous suture the catheter was connected to an aspirating-box via a glass connexion and short rubber tube. The pressure was first recorded on the manometer of the aspiration-box, representing the pressure in the space below the right dome of the diaphragm, and then all possible air was aspirated and the amount noted. The catheter was withdrawn as the final knot was tied, thus preventing any air leak. The final pressure immediately before withdrawal was always completely negative. In these studies either the Stott or the Maxwell aspirating-box was used, and similar results were obtained with both. Each patient was radiographed post-operatively to discover if emptying this space between liver and diaphragm prevented *all* post-operative air from being retained. The results of these 27 cases are shown in Table V. The grade of post-operative air for all these 27 cases was: none in two cases, grade 1 in four, grade 2 in 17, grade 3 in two, and grade 4 in two. Case B7 is shown as grade 3 pneumoperitoneum in view of the post-operative radiograph. In other cases the *x*-ray appearances have not been taken into account in the grading, and the amounts of air therefore represent minimum values.

These results again stress the fact that large amounts of air are left behind by chance; in 21 cases 100 ml. or more was retained, and in 16 of these the pressure under the diaphragm was positive. In three out of six of those with 60 ml. or less air the pressure was negative. The normal pressure in the subphrenic space is negative (Harley, 1955). Thus one of the effects of pneumoperitoneum would seem to be the abolition of this negative pressure. If the retention of air can be prevented the negative pressure under the diaphragm will be restored. It is probably abolition of the negative subphrenic pressure that leads to basal collapse.

Although air was present post-operatively in some cases, despite the aspiration, the amounts were small. In no case was a considerable pneumoperitoneum left, and in only one case was a moderate amount of air retained. The remaining cases with air demonstrated only traces or small amounts.

Methods of Avoiding Retention of Air

The method of closing the incision around a catheter and aspirating the air before completing the suture is a useful means of studying the problem, but not a practical method to adopt in all abdominal operations, as it necessitates special, although simple, apparatus, and adds a little extra time to the operations. To achieve the same effect other simpler methods were therefore tried:

1. The patient was tilted a few degrees head down to restore the liver to its true position under the diaphragm and obliterate the dead space between it and the lower costal wall; this replacement of the liver was aided manually.

2. The co-operation of the anaesthetist was obtained to "blow-up" the abdominal contents towards the incision as it was being closed, just as in closing a thoracotomy wound the lung is blown up.

3. As the peritoneum was being sutured it was tented as little as possible, to avoid leaving a space below it.

4. It is important for the surgeon and anaesthetist together to ensure that relaxation is cancelled and tone is returning to the abdominal muscles as the peritoneum is being closed.

These methods added nothing to the time or the difficulties of operating, and were employed in the remaining 10 cases in Series B. Post-operative radiographs showed that in one case a trace of air remained, but in the other nine cases there was no post-operative air; 6 of these 10 cases were gastric operations. These simple measures would seem to be a simpler and more effective means of avoiding the retention of air than closing around a catheter.

Effect of Post-operative Pulmonary Complications

The post-operative radiographs of the 37 cases in Series B showed clear lung fields in 16. Twenty showed pulmonary complications, half mild and half major, and the distribution of these changes is shown in Table VI. One case which showed congestive changes in the lungs due to temporary left ventricular failure is excluded.

TABLE V.—*Amounts of Air Aspirated From Right Subphrenic at End of Upper Abdominal Laparotomies, With Pressure of Each*

Case No.	Air Removed (ml.)	Initial Pressure (cm. H_2O)	Post-operative Pneumoperitoneum
1	None	− 4	None
2	None	− 2	,,
3	200	+ 4	,,
4	20	− 5	Grade 2
5	200	+ 1	,, 2
6	450	+ 9	None
7	180		Grade 3
8	220	+ 2	,, 2
9	1,000	+ 2	,, 1
10	100	+ 3	,, 1
11	300	+ 2	,, 1
12	1,140	+ 4	,, 2
13	200	+ 4	,, 1
14	20	+ 2	,, 1
15	240	+10	,, 2
16	40	+ 2	None
17	220	− 2	Grade 1
18	220	+ 2	,, 2
20	260	+ 4	None
21	390	+ 5	Grade 2
22	300	+ 2	None
23	60	+ 2	Grade 1
26	260	+ 2	None
28	220	Atmospheric	Grade 1
34	600	− 4	None
36	100	− 8	Grade 2
37	150	+10	None

By comparison with Table III, it can be seen that a significantly smaller proportion of Series B cases showed major complications than in the gastric group of Series A, and a larger number showed clear lung fields.

None of the eight non-gastric cases in Series B showed any post-operative air. The 18 cases with retention of air were all gastric operations, and the pneumoperitoneum grades and distribution are shown in Table VII.

It is interesting to note that the pulmonary complications occurring in Series B are fairly evenly distributed (Table VI), and do not show the strong tendency to be right-sided that appeared in the gastric operations of Series A. This may be associated with the fact that the post-operative air in Series B also showed less tendency to occur on the right (Table VII). Correlation between the occurrence of pneumoperitoneum and the appearance of post-operative pulmonary complications for the 37 cases of Series B is shown in Table VIII. From this it can be seen that the lower grades of pneumoperitoneum exert singularly little influence upon the chest complications; the larger amounts of pneumoperitoneum are missing—one only in grade 3 and none in grade 4.

The numbers studied justify fair comparison between the gastric operations of Series A and those of Series B in which post-operative air was greatly reduced in incidence and amount by the methods described. It has been shown that not only was the occurrence of post-operative pneumoperitoneum reduced but the rate of pulmonary complications, especially the major changes, was also lowered. Table IX shows the relative incidence of pulmonary changes in these two groups, and the figures are obtained from Tables III and VI.

The reduction of major pulmonary complications in Series B (28%) as compared with Series A (48%) is striking. The only varying factor in the two series was the deliberate reduction of post-operative pneumoperitoneum achieved in Series B.

The inevitable conclusion must be that the occurrence of post-operative pneumoperitoneum is associated with pulmonary complications, and that the avoidance of retention of air can lower the incidence of these chest conditions. It is not claimed that post-operative air is the only cause of pulmonary collapse, but the evidence here suggests that it is one of the factors concerned.

TABLE VI.—*Pulmonary Complications in 36 Cases in Series B*

Pulmonary Complications	Total	Right-sided	Left-sided	Bilateral
None	16			
Mild	12	4	4	4
Major	8	3	3	2

TABLE VII.—*Occurrence and Distribution of Post-operative Air in Gastric Operations of Series B (29 Cases)*

Pneumoperitoneum	Total	Right-sided	Left-sided	Bilateral
None	11			
Grade 1	9	4	2	3
,, 2	8	6	0	2
,, 3	1	1		
,, 4	0			
	29	11	2	5

TABLE VIII.—*Correlation of Post-operative Air and Pulmonary Complications in Series B*

Group	Pneumo-peritoneum	Pulmonary Complications		
		None	Mild	Major
Gastric operations (29)	None	6	4	1
	Grade 1	2	2	5
	,, 2	3	4	1
	,, 3	—	—	1
Non-gastric operations (3 upper abdominal, 4 lower abdominal, 1 pelvic)	None	5	2	—
	Grade 1	—	—	—
	,, 2	1	—	—
	,, 3	—	—	—

TABLE IX.—*Comparison of Incidence of Post-operative Pulmonary Complications in Gastric Operations of Series A and Series B*

	Pulmonary Complications		
	None	Mild	Major
Series A (47 cases) ..	32% (15)	19% (9)	49% (23)
,, B (29 cases) ..	38% (11)	34% (10)	28% (8)

Summary

In 82 patients undergoing abdominal operations, where the incidence of pneumoperitoneum was known (Bevan, 1961), the rate of post-operative chest complications has been ascertained by *x*-ray examination (Series A).

There is found to be a close correlation between post-operative pneumoperitoneum and pulmonary collapse.

In a second series of 37 cases, measures were taken to avoid leaving residual peritoneal air (Series B).

The group of gastric operations in each series (47 in Series A and 29 in Series B) are compared; the latter group, where large pneumoperitoneum has been avoided, show a greatly reduced incidence of major chest complications.

I am indebted to Professor F. A. R. Stammers for his help and encouragement; most of the patients studied were under his care. I owe much to the other members of the Surgical Unit at the Queen Elizabeth Hospital for helpful discussion and criticism, and I am indebted to the anaesthetists involved for the help they gave. I thank Dr. K. W. Cross for reading the manuscript, and Mrs. M. K. Mason for secretarial assistance.

The work owes much to the help and co-operation of Dr. O. E. Smith and his colleagues in the Radiological Department.

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The proceedings of the three-day Department of Scientific and Industrial Research Ergonomics Conference held in London last September have now been published. All the papers and a verbatim report of the delegates' discussions are included. Ergonomics, the scientific approach to the problem of fitting the job to the worker, is aimed at improving industrial efficiency by designing equipment so that its operation is within the mental and physical capacities of the average person. The purpose of the conference was to bring ergonomics to the notice of senior people in industry and to provide an opportunity to discuss its wider implications—in particular where ergonomics fits in with the interests of production engineering, equipment design, work study, and industrial health. (*Proceedings of Conference on Ergonomics in Industry, 27–29 September, 1960*, published for D.S.I.R. by H.M.S.O., price 12s. 6d. ($2.25 U.S.A.), by post 13s. 4d.)

RETROGRADE COLONIC SPREAD OF ENEMATA IN ULCERATIVE COLITIS

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Intrarectally introduced solutions are being increasingly used in the treatment of ulcerative colitis. Small amounts (100–120 ml.) of therapeutic solutions are being introduced into the rectum by the slow-drip method of Truelove (1956, 1957) and by the single-dose retention enema (Matts 1960a). In addition, small-volume evacuant enemata are being widely employed in nursing practice, using disposable plastic bags.

Although these techniques are widely used, many people are unaware of the degree of penetration of the solutions so introduced. It therefore seemed important to demonstrate the extent of retrograde spread of these solutions. A simple and fairly convincing way of doing this is by introducing a radio-opaque solution into the rectum.

Present Investigation

Objectives.—(1) To determine the extent of penetration of intrarectally introduced solutions, using the enema-bag method, in patients with ulcerative colitis (Matts, 1960a, 1960b). (2) To determine the extent of penetration of intrarectally introduced solutions, using the slow-drip method of Truelove (1956, 1957, 1958, 1959), in patients with ulcerative colitis. (3) To compare these two methods and consider the possible advantages of one or other method from the viewpoint of therapeutic application. (4) To determine the penetration of intrarectally introduced solutions, using the enema-bag method, in normal people. This was undertaken to see whether there was any difference in penetration in normal people as opposed to those with ulcerative colitis. It was also felt to be of value to know the retrograde penetration in normal people in view of the increasing prevalence of the use of these disposable plastic enema bags as evacuant enemata in district-nursing procedures, etc. (over 100,000 of these were sold in 1959 according to the figures of one manufacturer).

Method.—Patients who were to have barium-enema examinations either for ulcerative colitis or for other reasons formed the subjects of the investigation. They were brought to a special radiological clinic and initially were given either the enema bag or the slow-drip infusion. Screening and the taking of films were followed by a normal barium-enema examination. Thus up-to-date information was immediately available, for diagnostic or confirmatory purposes, of the type and extent of disease, if any.

Technique

A 40% suspension of barium in water was employed as a radio-opaque solution without any additive. The plastic enema bag was filled with 100 ml. of the barium suspension and inserted into the rectum in the same way as the therapeutic solutions were given. The patient was on the left side and was rolled over on to the abdomen after the injection was finished, in exactly the same way as the patients using the therapeutic enemata were instructed to do. Screening was performed and films were then taken.

If the patients were to be tested with the drip technique the apparatus was first set up as illustrated by Truelove (1959). Then 100 ml. of barium was put into the infusion bottle and the intrarectal catheter inserted. The solution was then slowly run in as Truelove (1956, 1957, 1958, 1959) recommended. When it was all run in the patient was rolled on to the abdomen for two to three minutes so that conditions were exactly comparable to the enema-bag technique and screening was performed and films were taken.

Patients who were having a routine screening barium-enema examination to exclude other disease were used as the normal controls. They were counted in the series only if the subsequent barium-enema examination confirmed that their colons were radiologically normal. The enema-bag technique used was exactly the same as that previously described for the ulcerative-colitis patients.

In all, 10 patients were investigated in each group, making a total of 30. The ulcerative-colitis patients were unselected and the decision whether to use drip or enema bag was made by random selection.

Results in Ulcerative-colitis Patients

With Plastic-Bag Administration of Radio-opaque Solution.—In order to save space, films of only two patients are shown (Figs. 1 and 2). These are representative of the best and the worst penetration of the series. Figs. 1 and 2 and the Table clearly show that the solution introduced into the rectum by the single-dose enema-bag technique penetrates a long way up the colon. The least retrograde penetration found was nearly to the splenic flexure and the most was to the ascending colon. This clearly shows that much of the

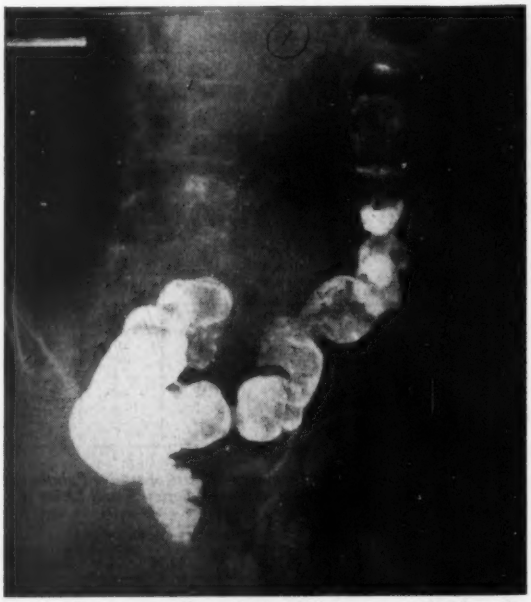

FIG. 1.—Least penetration of colon with bag enema in ulcerative colitis.

colon comes within the field of operation of intrarectally introduced solutions, and this fact is of importance in considering their therapeutic application.

With Slow-drip Infusion of Radio-opaque Solution.—Again two patients' films are illustrated (Figs. 3 and 4), and the full results are shown in the Table. These films show that a similar degree of penetration can be achieved by this method to that obtained with the enema bag. The only difference was that in two patients of the series the penetration was only as far as the rectum, so possibly the most adverse result, in terms of penetration, may be worse by this method than by the enema-bag method.

FIG. 2.—Most penetration of colon with bag enema in ulcerative colitis.

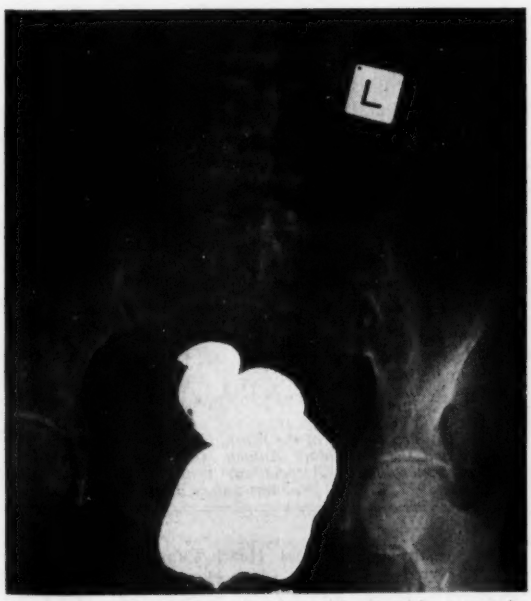

FIG. 3.—Least penetration of colon with slow-drip enema in ulcerative colitis.

Extent of Retrograde Penetration Into the Colon According to Method of Administration and Presence or Absence of Ulcerative Colitis

Retrograde Penetration as far as—	Ulcerative-colitis Patients		Patients Without Colonic Disease
	Single Dose from Enema Bag	Slow-Drip Infusion	Single Dose from Enema Bag
Caecum	0	0	0
Ascending colon	2	2	0
Hepatic flexure	2	0	0
Mid-transverse colon ..	3	2	0
Splenic flexure	1	2	2
Mid-descending colon ..	2	1	4
Sigmoid ,, ...	0	1	4
Rectum only	0	2	0
Total ..	10	10	10

Results in Patients Without Ulcerative Colitis and With Radiologically Normal Colons

Representative films from two patients are shown in Figs. 5 and 6, and the full results are given in the Table. A possible significant difference is here seen. The degree of penetration is not so great in these patients as in those with ulcerative colitis. Out of the 10 patients investigated only two have comparable films, from a viewpoint of penetration of the solution, to that seen in ulcerative-colitis patients. All the others show much less retrograde spread of the injected radio-opaque solution up the colon. A possible explanation for this is that the colon in ulcerative colitis lacks tone and thus offers less resistance to retrograde spread. Alternatively, the loss of haustrations (often absent radiologically in ulcerative colitis) may mean that downward peristaltic activity is less marked, and this is the cause of the lessened resistance to the upward flow of intrarectally introduced solutions.

Of course, it is possible that this is a coincidental finding due to the small number of cases in the series. However, it seems striking enough to warrant some speculation into its cause and also, perhaps, to justify further investigation in the future.

FIG. 4.—Most penetration of colon with slow-drip enema in ulcerative colitis.

Discussion of Results

It is clear from the results of this radiological investigation that single-dose plastic-enema-bag administration of solution into the rectum gives good results, especially in ulcerative colitis. From a therapeutic point of view one can expect a minimum penetration of the solution up to the mid-descending colon. In many cases penetration retrogradely will occur as far as the splenic or hepatic flexures. This brings a good part of the colon into the range of solutions administered intrarectally. This is a very important finding and demonstrates the range of useful clinical application of intrarectal therapeutics. It must be remembered that one is using a suspension of barium in this investigation. This does not diffuse readily owing to its fairly high viscosity; thus it seems reasonable to suggest that an actual aqueous solution of prednisolone, with its lower viscosity, should diffuse further and thus give greater retrograde colonic penetration. This postulation is supported by results of the therapeutic solution's effectiveness in a few cases of generalized ulcerative colitis (Matts, 1961).

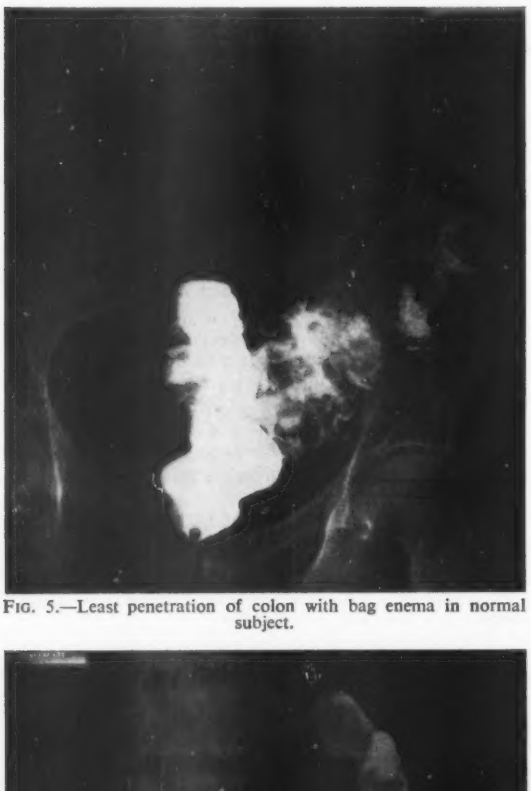

FIG. 5.—Least penetration of colon with bag enema in normal subject.

FIG. 6.—Most penetration of colon with bag enema in normal subject.

Comparison of drip and single-dose-enema techniques shows little advantage either way. This clearly refutes suggestions that the slow drip method is a necessary part of intrarectal therapeutic technique due to failure of penetration of a fairly rapid one-dose administration. If anything, the single-dose method shows more consistent retrograde penetration into the colon.

The coincidental finding of less penetration of the normal colon as opposed to that of sufferers from ulcerative colitis has already been discussed. It is important to realize how far back solutions inserted into the rectum are apt to get. This may influence formulation of the solutions used in the evacuant plastic-bag enemata that are being widely employed these days in district nursing and obstetric work. Some solutions that are harmless when only expected to be in the rectum may have adverse effects if they penetrate far into the colon.

Summary

A radiological investigation has been conducted into the degree of penetration of intrarectally introduced solutions into the colon.

This shows that penetration can sometimes be achieved as far as the ascending colon with only 100 ml. of radio-opaque suspension. In most sufferers from ulcerative colitis the left side of the colon can easily be reached.

No significant difference was shown between the slow drip and the single-dose plastic-enema-bag method of administration.

In people not suffering with ulcerative colitis the degree of retrograde spread was less. Reasons for this are briefly discussed.

Ulcerative colitis by its nature therefore seems to lend itself to intrarectal therapy.

The significance of the degree of penetration of intrarectal solutions is briefly discussed with respect to the plastic-bag evacuant enemata used in many nursing procedures.

We thank Dr. J. M. Naish for permission to carry out the investigation on his patients, and Messrs. Fletchers and Harker Stagg for supplies of enema bags.

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The Australian National Heart Campaign has raised £A2,250,000 for research—£¼m. more than the national target. The appeal, which ended recently, was carried out by 200,000 collectors throughout Australia.

PYRIMETHAMINE IN THE TREATMENT OF POLYCYTHAEMIA RUBRA VERA

BY

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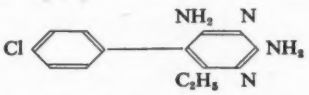
Polycythaemia rubra vera has been treated by venesection, haemolytic drugs, irradiation, and occasionally by alkylating agents. Irradiation by means of injected radiophosphorus (^{32}P) is probably the most widely used treatment at the moment. The introduction of chemical inhibitors of nucleic-acid synthesis has provided yet another method of suppressing the hyperactive erythron in this disease. This paper describes our experience of one such drug—pyrimethamine.

Hitchings *et al.* (1948) showed that many aminopyrimidines inhibit the growth of *Lactobacillus casei* by preventing the utilization of folic acid. The discovery of the association between antimalarial action and folic-acid antagonism in the case of proguanil (Falco *et al.*, 1949) led to the investigation of the aminopyrimidines as possible antimalarial agents. The most active aminopyrimidine was found to be 2-4-diamino-5(4-chlorophenyl)-6-ethylpyrimidine (Falco *et al.*, 1951). This drug was called "daraprim" and has received the official name of pyrimethamine.



Pyrimethamine has proved to be a valuable agent in malarial prophylaxis (Vincke and Lips, 1952), and when combined with sulphadiazine is effective against toxoplasmosis (Frenkel and Hitchings, 1957).

Hamilton *et al.*, (1952) reported that the administration of diaminopyrimidines of this type to rats and dogs produced a megaloblastic anaemia with leucopenia. A detailed study of the pharmacology of pyrimethamine was reported by Schmidt *et al.* (1953), who found that the compound was extremely toxic in high doses, but their data indicated that erythropoietic depression might be obtained at doses low enough to avoid serious effects on other systems.

Isaacs (1954) was the first to report the use of pyrimethamine in the treatment of polycythaemia rubra vera. He produced depression of the red-cell count without leucopenia or thrombocytopenia in six patients receiving 12.5–25 mg. daily. A time lag of two to three weeks in the response of the red-cell count was noted. Subjective and objective improvement was obtained in all cases. Frost and Jones (1954) recorded the treatment of six patients receiving 15–25 mg. a day. Satisfactory clinical and haematological remissions occurred in all cases, and side-effects were not reported.

Wasserman (1955), however, condemned the use of pyrimethamine in the management of polycythaemia. He found the response to be slow, unpredictable, and unsatisfactory in at least 80% of cases, while side-effects were prominent and troublesome. Leucopenia, thrombocytopenia, petechial and gastro-intestinal haemorrhage, nausea and vomiting, buccal ulceration, and bone-marrow aplasia were all reported.

Materials and Methods

This series consists of five patients presenting consecutively with polycythaemia rubra vera in relapse. Four had previously been treated with ^{32}P. One patient received two courses of pyrimethamine. The haemoglobin concentration and leucocyte count were measured at intervals of one to four weeks in Cases 1 to 3. Cases 4 and 5, and Case 3 during the second course of treatment, were subjected to more detailed study which included estimates of the haemoglobin concentration, packed cell volume, and red-cell, reticulocyte, leucocyte, and platelet counts. These were performed at weekly intervals on sequestrinated venous blood, using the techniques described by Dacie (1956), absolute erythrocyte values being calculated on each occasion. When the haemoglobin concentration had returned to normal, tests were carried out at two-weekly intervals. Red-cell mass, red-cell life, and plasma-iron-clearance rates were measured before and during treatment, using the ^{51}Cr and ^{59}Fe techniques described by Ebaugh *et al.* (1953) and Wetherley-Mein *et al.* (1956).

Initially, pyrimethamine was administered in 25-mg. scored tablets. Later, an elixir containing 6.25 mg./ml. became available and was used in Case 3(b).

Case 1

A man aged 60 presented in January, 1953, with dyspnoea, plethora and cyanosis, headaches, and giddiness. The tip of his spleen was palpable 1½ in. (3.8 cm.) below the costal margin. Investigations confirmed the diagnosis of polycythaemia rubra vera. Treatment was initially by venesection, but later two doses of ^{32}P were administered. However, in October, 1958, five and a half years later, he was again in relapse.

Investigations.—Haemoglobin, 21.9 g./100 ml.; erythrocytes, 7,500,000/c.mm.; leucocytes, 6,700/c.mm.; platelets, 260,000/c.mm.

Treatment.—Pyrimethamine was administered by mouth in doses ranging from 25 to 200 mg. a day. Fig. 1 demonstrates the difficulty experienced in establishing the daily dose of pyrimethamine necessary to maintain the haemoglobin concentration within normal limits. The leucocyte count tended to fall on a daily dosage exceeding 50 mg., and to rise above normal on sudden reduction of dosage. The time interval for leucocyte response was much shorter than that for haemoglobin concentration.

The patient became symptom-free after eight weeks' treatment and has remained so up to the time of writing,

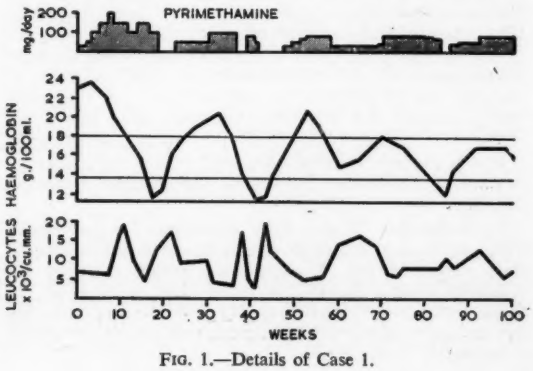


FIG. 1.—Details of Case 1.

a period of two years. He experienced some epigastric discomfort at doses exceeding 100 mg. daily, and vomited once during the week in which he received 200 mg. a day. There were no other side-effects.

Case 2

A man of 56 presented in 1954 with a one-year history of progressive facial rubor and giddiness. He was found to be plethoric, with enlargement of the spleen to the umbilicus. Investigations confirmed the diagnosis of polycythaemia rubra vera. During the next three years the disease was controlled by three doses of ^{32}P; but one year later, in 1958, he was again in relapse with severe giddiness and hepatosplenomegaly.

Investigations.—Haemoglobin, 20.8 g./100 ml.; erythrocytes, 8,000,000/c.mm.; leucocytes, 6,000/c.mm.; platelets, 300,000/c.mm.

Treatment.—Pyrimethamine was administered in daily doses of 25 to 75 mg. for one year, at which time he was lost to follow-up. Fig. 2 illustrates the satisfactory nature of the response obtained, the patient becoming asymptomatic in five weeks and remaining so throughout the treatment.

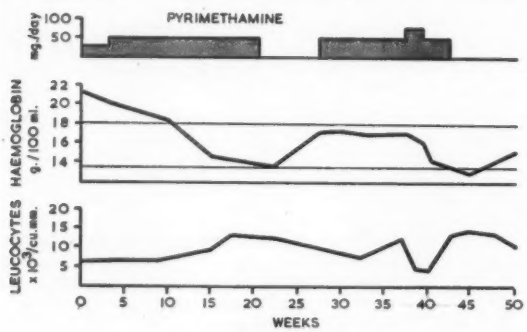


FIG. 2.—Details of Case 2.

It soon became clear that 50 mg. of pyrimethamine a day just exceeded the optimum dose for adequate control of erythropoiesis. Two brief interruptions of treatment at this dosage controlled the disease very satisfactorily for one year. He experienced some epigastric discomfort during treatment. This was unrelated to the dosage of pyrimethamine and was proved to be due to an exacerbation of long-standing peptic ulceration. It responded completely to antacids.

Case 3

A man aged 65 presented in October, 1954, with myocardial infarction. He was plethoric and his spleen had enlarged to the umbilicus, while the liver edge was palpable 1 in. (2.5 cm.) below the costal margin. The haemoglobin level was 18.2 g./100 ml. No treatment for the polycythaemia was given at this date. Eighteen months later he developed thromboses in his right upper and left lower limbs, and examination revealed other features characteristic of polycythaemia rubra vera. During the ensuing year he received two injections of ^{32}P with satisfactory results, but in 1959, two years after the second injection, he was once more in relapse with severe symptoms.

Investigations.—Haemoglobin, 18.3 g./100 ml.; erythrocytes, 6,300,000 c.mm.; leucocytes, 14,900/c.mm.; platelets, 350,000/c.mm.

Pyrimethamine 50 mg. daily was given for two weeks. This produced a profound fall in haemoglobin concentration, shown in Fig. 3, and a sharp depression of the leucocyte count. It will be noted that recovery of the haemoglobin concentration started two months later, but the leucocyte count recovered much more rapidly, producing a temporary leucocytosis.

Comments on Cases 1–3

A marked feature of these three cases is the wide range of doses necessary to maintain normal haemoglobin levels. Thus Case 1 required somewhere between 62.5 and 75 mg. a day, Case 2 just under 50 mg. a day, while the dose for Case 3 was evidently very much less than 50 mg. a day and probably less than 20 mg. It is also evident from Figs. 1–3 how difficult it is to establish the correct dosage from the slowly responding haemoglobin level. Although the leucocyte count tended to respond more rapidly it lacked sensitivity and was subject to variations independent of drug dosage.

In the normal subject the red-cell mass is regulated within 30% limits, but in polycythaemia rubra vera there is an excess of 30–200%. Since the life-span of the erythrocyte is unaltered the bone-marrow production rate must also be increased by 30–200%. If we consider a typical example where the red-cell mass is twice the normal value the object of treatment is twofold, firstly, to reduce the red-cell mass by 50%, and, secondly, to decrease red-cell production by 50%. If both of these objects are to be achieved by controlled suppression of nucleic-acid synthesis such that erythropoiesis is exactly halved, it follows that a period of time equal to the red-cell life (16 weeks) will elapse before the red-cell mass is normal. We have assumed that it is possible to adjust drug dosage precisely enough to achieve such an effect, but in fact, as we have seen, individual variation in dose response is so large that a measure of individual drug requirement is indispensable. A measure dependent on the red-cell mass—for example, the haemoglobin concentration—is not satisfactory because of the very long time interval which will elapse before a reliable estimate of the effectiveness of the drug dosage can be made.

In view of these problems it was decided to subject future cases to more detailed haematological study.

Case 4

A woman aged 69 presented with headache, tiredness, epistaxis, and facial rubor increasing over a period of three months. Physical examination showed marked plethora, with cyanosis of the face and lips, and congested conjunctival vessels. The spleen was palpable 1½ in. (3.8 cm.) below

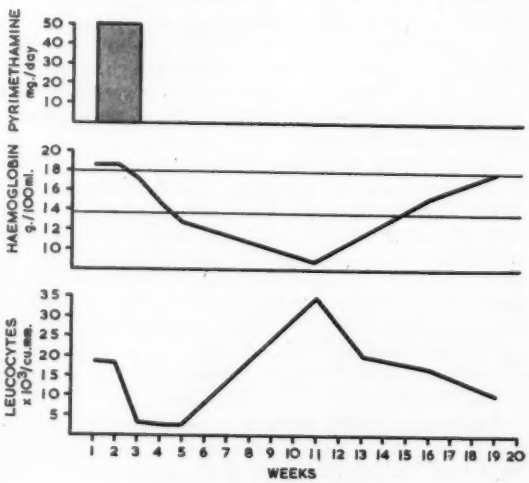


FIG. 3.—Details of Case 3.

the costal margin. She was mildly hypertensive (B.P. 150/100) with grade 1 retinopathy.

Investigations.—Haemoglobin, 23.7 g./100 ml.; erythrocytes, 9,400,000/c.mm.; reticulocytes, 120,000/c.mm. (normal 20,000–100,000 c.mm.); leucocytes, 11,100/c.mm. (differential count normal); platelets, 400,000/c.mm.; red-cell mass, 82 ml./kg. (normal 20–40 ml./kg.); mean cell volume, 79 cubic microns; plasma iron clearance T/2= 18 minutes (normal 70–130 minutes). Sternal marrow biopsy: normoblastic proliferation with hyperplasia of the myeloid series and megakaryocytes.

Treatment.—Pyrimethamine 25 mg. daily by mouth was administered for two weeks, after which the dose was increased to 50 mg. daily for a further two weeks. Fig. 4 shows that this depressed the reticulocyte and platelet counts to very low levels, and after two weeks the red-cell count and haemoglobin concentration began to fall. The erythrocytes showed marked anisocytosis with numerous macrocytes, causing the mean corpuscular volume to rise above normal. Thrombocytopenia was accompanied by slight epistaxis and several ecchymoses. Erythrocyte survival measured during the first month of therapy indicated a normal life-span (^{51}Cr T/2=30 days), and at the end of this period the red-cell mass had fallen to 73 ml./kg. and the iron clearance rate T/2 was 132 minutes. Pyrimethamine was withheld for the next two weeks, during which time the haemoglobin and erythrocyte levels continued to fall, but the reticulocyte and platelet counts recovered after one week. After a further week therapy was resumed at the lower dose rate of 12.5 mg. daily. Within two weeks the haemoglobin concentration and erythrocyte count were within normal limits, and after two months the red-cell mass was 40 ml./kg. Sternal bone-marrow biopsy revealed hyperplasia with many intermediate megaloblasts. The mean corpuscular haemoglobin concentration was not significantly altered by the treatment.

The patient began to feel better two weeks after starting treatment and was symptom-free within two months. The spleen decreased in size but remained palpable after seven months of treatment. Her drug requirement has been in the range of 6–12 mg. a day.

Case 5

A man aged 64 presented in March, 1956, with giddiness, plethora, and generalized pruritus. The spleen was not palpable, but investigation of the peripheral blood and bone-marrow confirmed the diagnosis of polycythaemia rubra vera. Satisfactory control was achieved with two doses of ^{32}P during the next four years, but in 1960 he was again in relapse.

Investigations.—Haemoglobin, 19.7 g./100 ml.; erythrocytes, 6,900,000/c.mm.; reticulocytes, 130,000/c.mm.; leucocytes, 6,100/c.mm. (differential count normal); platelets, 218,000/c.mm.; red-cell mass, 46.5 ml./kg.; mean cell volume, 93 cubic microns; plasma iron clearance T/2= 33 minutes. Sternal marrow biopsy: normoblastic proliferation with hyperplasia of the myeloid series and megakaryocytes.

Treatment.—Pyrimethamine 50 mg. daily was given for one month. This produced a fall in the reticulocyte and platelet counts as shown in Fig. 5. The haemoglobin concentration began to fall after two and a half weeks. The peripheral blood then showed gross anisocytosis with many macrocytes, the mean cell volume having risen to 115 cubic microns. The dose was then reduced to 12.5 mg. a day, but the subsequent rise in reticulocyte count first to 34,000/c.mm., and then, one week later, to 120,000/c.mm., caused us to increase the daily dosage to 25 mg. During the ensuing three months the haemoglobin level and erythrocyte, leucocyte, and platelet counts remained within normal limits and the reticulocyte count between 40,000 and 60,000/

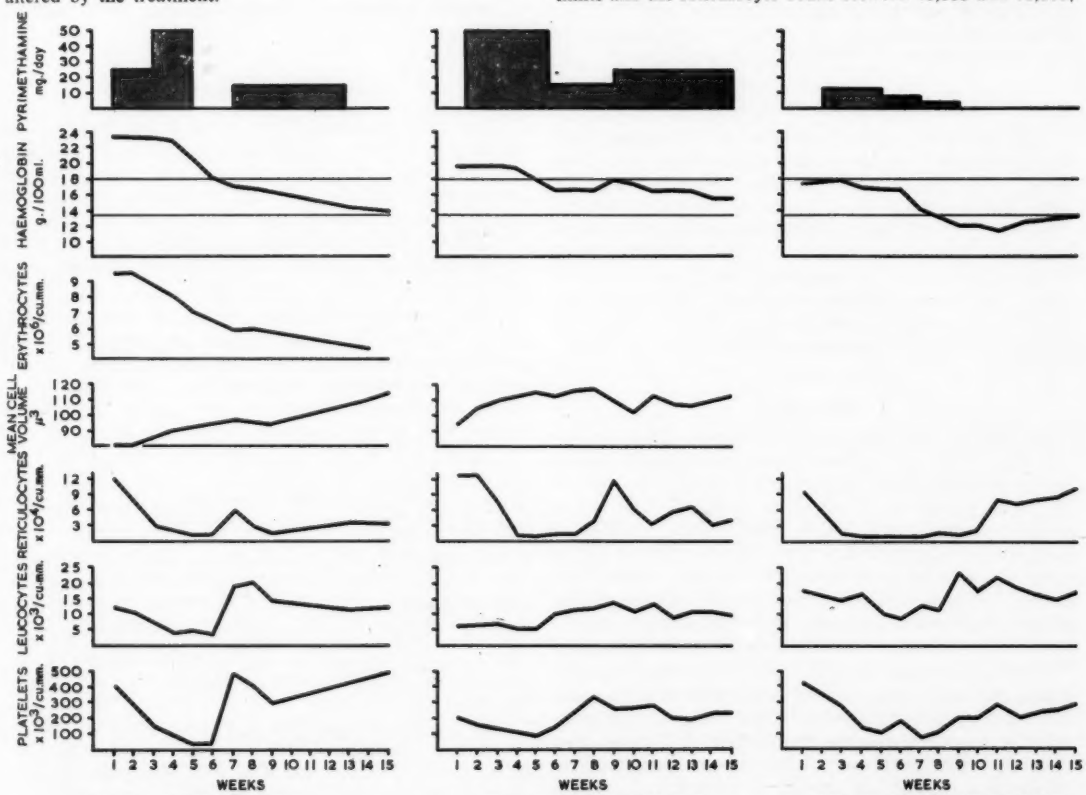


FIG. 4.—Details of Case 4.

FIG. 5.—Details of Case 5.

FIG. 6.—Details of Case 3(*b*).

c.mm. Sternal aspiration biopsy revealed a hyperplastic marrow with numerous intermediate megaloblasts. Erythrocyte survival measured during treatment was normal (^{51}Cr T/2=29 days) and the M.C.H.C. was not significantly altered. The plasma iron T/2 was prolonged to 71 minutes.

The patient remained well throughout the treatment, experiencing only minimal abdominal discomfort while taking 50 mg. of pyrimethamine daily. No other side-effects were noted.

Case 3(b)

This is the same patient as in Case 3, receiving a second course of pyrimethamine five months after his first treatment.

Investigations.—Haemoglobin, 17.7 g./100 ml.; erythrocytes, 5,000,000/c.mm.; reticulocytes, 100,000/c.mm.; leucocytes, 17,700/c.mm. (differential count normal); platelets, 415,000/c.mm.; red-cell mass, 43.5 ml./kg.; mean cell volume, 116 cubic microns; plasma iron clearance T/2= 15 minutes. Sternal marrow biopsy: normoblastic proliferations with hyperplasia of the myeloid series and megakaryocytes.

Treatment.—Cautious treatment with pyrimethamine was resumed at a dosage of 12.5 mg. daily for three weeks. This depressed the reticulocyte count to 5,000/c.mm. as shown Fig. 6. The haemoglobin concentration and leucocyte and platelet counts were also depressed. Administration of the drug was continued for the next month at gradually reducing dosage and then stopped. The haemoglobin level continued to fall while the platelet and reticulocyte counts recovered.

In the seven months which have elapsed since this course of pyrimethamine three brief periods of drug treatment at doses of 3–6 mg. daily have been required to maintain a complete remission. The mean cell volume has remained between 110 and 120 cubic microns, the M.C.H.C. was within normal limits, and the life-span of his erythrocytes was normal during treatment (^{51}Cr T/2=30 days).

Comments on Cases 4, 5, and 3(b)

The reticulocyte count provided the earliest and most sensitive index of erythropoietic depression in these three cases. For maintenance purposes it seemed that the dose which maintained a count of 30,000 to 60,000/c.mm. (0.6–1.2%) resulted in a stable haemoglobin level. Although thrombocytopenia occurred initially in all three cases, it was not produced by this maintenance dose. Similarly, although epigastric discomfort and anorexia occurred at high dosage in Case 5, there were no side-effects at maintenance dosage in any patient.

Discussion

In each of the five cases continuous administration of pyrimethamine produced a steady fall in the haemoglobin concentration, packed cell volume, and red-cell count of peripheral blood after an initial time lag of two to three weeks. This effect was not due to haemolysis, since measurement of the red-cell life in three cases under treatment gave normal values. The early depression of the reticulocyte level and the slowing of the plasma-iron-clearance rate demonstrate conclusively that there is a marked reduction in red-cell output.

During treatment the erythrocytes showed gradually increasing anisocytosis and macrocytosis, with the mean cell volume rising to 110–120 cubic microns, and bone-marrow smears presented the picture of "maturation arrest" with numerous intermediate megaloblasts. These observations are consistent with the suggestion that the principal effect of this drug is to inhibit the conversion of folic acid to folinic acid (Hitchings *et al.*, 1952). Megakaryocyte activity and myelopoiesis are also depressed at high dosage, but platelet and leucocyte levels were not affected by maintenance doses of pyrimethamine and side-effects were completely absent. Unlike Wasserman, we failed to observe a single instance of alopecia, buccal ulceration, gastro-intestinal haemorrhage, or bone-marrow aplasia, although particular attention was paid to these possibilities. Anorexia, epigastric discomfort, nausea, and vomiting were produced in two cases receiving higher doses. Similarly, ecchymosis and epistaxis occurred in one case receiving large doses of pyrimethamine.

The main problem has been that of deciding the correct dosage for each case—an important matter, since the side-effects which could be produced by excessive dosage are both unpleasant and dangerous. However, it has been practicable, using the rapidly responding reticulocyte count, to select the correct dose for each patient quite quickly, and it has been comforting to find that each patient behaved consistently according to his individual "sensitivity" and did not develop tolerance to the drug in the period under study. It is not clear whether there is a true variation in tissue sensitivity to the drug or whether the rate and extent of absorption are the variable factors. The animal studies of Schmidt *et al.* (1953) suggest that the rate of intestinal absorption may be one important variable. Once the patient's correct dose has been found, many weeks will elapse before a normal haemoglobin level is restored. It is dangerous to accelerate this process by using large doses of pyrimethamine, but, if the severity of the symptoms demand it, venesection may save valuable time.

Summary and Conclusions

Five cases of polycythaemia rubra vera treated with pyrimethamine for periods of seven months to two years are presented. Excellent clinical and haematological remissions were obtained and maintained in all cases with minimal side-effects. The wide variation in individual response to the drug is stressed and the value of the reticulocyte count as a rapid and sensitive index of drug requirement is emphasized.

Oral pyrimethamine provides an effective treatment for polycythaemia rubra vera, but its potential toxicity necessitates meticulous haematological control, particularly at the beginning of treatment. Side-effects have been consistently absent at the correct therapeutic dosage; in this respect our experience resembles that of Isaacs (1954) and of Frost and Jones (1954), and differs greatly from that of Wasserman (1955). It is indeed difficult to understand how such gross toxic effects could be produced at therapeutic dosage.

We thank Dr. K. A. Newton, who suggested this study and who has provided constant advice and encouragement. We are grateful to the Medical Committee of Westminster Hospital, and to Dr. S. P. Meadows and Dr. C. J. Gavey for permission to publish details of patients under their care. Our thanks are also due to Dr. P. Hansell for the illustrations and to Dr. J. G. Humble and Dr. N. H. Kemp for helpful discussions.

The cost of the apparatus used in this study was met by a generous donation by Mr. Geoffrey Harmsworth. One of us (D. E. P.) was in receipt of a full-time grant from the British Empire Cancer Campaign during the period of this study.

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SEASONAL INCIDENCE OF CLINICAL ONSET OF HODGKIN'S DISEASE

BY

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In reviewing 269 cases of histologically proved Hodgkin's disease seen at the Royal Marsden Hospital since 1945, a high incidence of clinical onset in the month of December was observed.

Criteria for Selection

Since the mode of onset is so variable and the presenting symptoms may appear long after the true onset of the disease, a seasonal association could have significance only if the clinical onset were closely related in time to the apparent onset of the disease. In 106 cases there is reason to suppose this was so, and the following criteria were used in selecting them: (1) the month of onset was definitely stated; (2) lymphadenopathy was localized to one peripheral site at onset; (3) no evidence of generalized disease was present; (4) disease was confined to superficial lymph nodes with no clinical or radiological evidence of deeper involvement within six months of onset; and (5) patients were living in England at the time of onset.

Time of Onset.—In many cases the time of appearance of the first enlarged lymph node was remembered precisely by the patient, sometimes to within a few days. If the onset was remembered to within one calendar month the case was accepted for analysis, but when the description was less precise, as, for example, "about nine months ago," the case was excluded.

Site.—In 70 of the 106 patients the disease remained strictly localized to one region for six months or more. Of the remaining 36 patients, some developed enlarged nodes in the corresponding region on the opposite side, and a few had axillary involvement on the same side after initial cervical-node involvement. Provided the disease remained localized to these sites for at least six months, the case was included in the series. If the mediastinum, for instance, was the true site of onset, although the appearance of enlarged cervical nodes was the first clinical evidence of disease, some evidence of a mediastinal lesion might have been expected to be manifest within six months.

Cases Excluded from the Series

Criteria for exclusion of cases were as follows. (1) Generalized peripheral lymphadenopathy at the time of clinical onset (3 cases). (2) Evidence of intrathoracic or intra-abdominal involvement at the time of presentation or within six months (37 and 9 cases respectively), or of paravertebral involvement (3 cases). (3) Localized disease for six months or more, but the month of onset not stated (24 cases). (4) Cases lost to follow-up within six months of the onset of the disease (1 case). (5) Onset of disease outside England (30 cases).

Constitutional symptoms such as fevers, sweats, lassitude, pruritus, or loss of weight were present in some cases, sometimes for several months, before Hodgkin's disease was diagnosed. These symptoms did not occur prior to the lymphadenopathy in the cases selected for the series.

A further 56 patients whose disease was clinically localized at the time of onset have been excluded from analysis because one or more of the following features were present: (1) peripheral lymphadenopathy in areas remote from the site of presentation within six months of clinical onset but without evidence of deeper involvement; (2) probable or early paratracheal or mediastinal spread not detected by serial *x*-ray films until five to six months after the first appearance of cervical nodes; (3) splenomegaly detected between three and six months after the onset of the disease; and (4) febrile episodes in the absence of other signs of spread of the disease within six months which, in retrospect, could have been due to subsequently discovered deep-seated disease not apparent at the time.

Although these 56 cases were not included in the series, they show almost exactly the same seasonal incidence as the 106 acceptable cases. If they were added to the 106, making a total of 162 cases, and the results compared with those of the 106 cases shown in Table I, the difference in incidence in any one month would be little more than $\pm 1\%$.

Many cases have thus been excluded because of the possibility that the disease was present for some time before the appearance of the first sign or symptom. Since rapidly progressive disease may develop from a focal lesion, some eligible cases might have been unnecessarily excluded.

Thus, of 269 case histories reviewed, 106 (39.5%) were regarded as suitable to be analysed for a possible seasonal association.

Results

Of the 106 patients selected, 23 (21.7%) had the clinical onset of Hodgkin's disease in the month of December. The results are shown in Table I.

Seasonal Incidence in the Two Periods 1945–53 and 1954–9.—To examine the seasonal incidence in different periods the 50 patients whose disease began in the period 1945–53 and the 56 whose disease began in 1954 to 1959 have been analysed separately. Table I shows that the seasonal incidence is essentially the same for each period and the whole period.

Incidence of Infection of the Upper Respiratory Tract at Clinical Onset of Hodgkin's Disease.—In the majority of cases the disease presented simply with painless

enlargement of a lymph node. It is possible that the high incidence of the disease in December was due to the prevalence of upper respiratory infection in that month. Patients might notice enlarged nodes for the first time if these or neighbouring nodes became tender in association with a septic throat. Of the 269 patients, 28 (10.4%) gave a history of sore throat or coryza just preceding or coincident with the finding of enlarged lymph nodes; 11 of these 28 are included in the series of 106 (10.4%). The monthly incidence of these patients presenting with respiratory infections is shown in Table II, from which it is seen that the simultaneous onset of enlarged nodes and upper respiratory infection was less common in December than in June. Five of the 11 patients have been questioned again and all are certain that enlarged nodes were not present before, but appeared during the infection and remained enlarged after it had subsided. Two cases of sore throat occurred in association with involvement of inguinal nodes only. Three patients complained of tender nodes initially. One, in December, had tenderness at the site of the presenting node several days prior to its enlargement. The two other patients, both with inguinal node involvement presenting in November and August, had rapidly enlarging tender nodes.

Possible Influence of Treatment Within the First Six Months.—The management of the 106 patients during the first six months after clinical onset of Hodgkin's disease is summarized in Table III. It is not possible in these cases to assess with certainty the influence of treatment on the recurrence rate within six months. From Table III it is seen that 38 patients were not treated within six months of the clinical onset of their disease. Their subsequent course was not less favourable than it was in the 68 patients treated sooner. It is more difficult to decide how far regional " prophylactic " irradiation or chemotherapy influenced the length of the first remission. It is, however, possible that more extensive initial treatment could have postponed recurrence which otherwise might have occurred within six months. Some of the 26 patients who received regional radiotherapy or chemotherapy or both might not have qualified for inclusion in the series if they had not received such treatment. If these 26 patients are excluded from the series, however, the percentage incidence of the time of onset is altered materially only in the month of September (7.5% instead of 11.2%).

Seasonal Recurrence Rate.—The onset of recurrence is usually impossible to establish because the majority of patients relapse with involvement of deeper regional nodes, which are often very large before their presence is detected. Nevertheless the month of relapse was noted in 89 patients, apparently in good health, who had recurrence in peripheral lymph nodes. No striking seasonal incidence was apparent.

Control Series.—A satisfactory control series is difficult to compile. In leukaemia, for example, an abnormal blood picture may have been present for a long time before symptoms arose or the disease was diagnosed. A survey has been made applying the same criteria for selection to 134 cases of lymphosarcoma (excluding those with lymphocytic leukaemia) and 50 cases of reticulosarcoma. The clinical onset could be established with precision in only 48 cases (26%). The onset of the disease in the 48 cases selected showed no particular seasonal incidence.

It is of interest to note that during the collection of data on Hodgkin's disease the preponderance of patients presenting in December was apparent when records of only 50 of the 106 selected cases had been examined.

TABLE I.—*Seasonal Onset of Hodgkin's Disease in* 1945–59 *and During* 1945–53 *and* 1954–9

Month of Onset	1945–59 (106 Cases)		1945–53 (50 Cases)		1954–9 (56 Cases)	
	No.	%	No.	%	No.	%
January ..	14	13·2	7	14·0	7	12·4
February ..	6	5·7	1	2·0	5	8·9
March ..	4	3·8	3	6·0	1	1·8
April ..	9	8·5	4	8·0	5	8·9
May ..	7	6·6	4	8·0	3	5·4
June ..	7	6·6	4	8·0	3	5·4
July	4	3·8	2	4·0	2	3·6
August ..	6	5·7	3	6·0	3	5·4
September ..	12	11·2	5	10·0	7	12·4
October ..	5	4·7	2	4·0	3	5·4
November ..	9	8·5	3	6·0	6	10·7
December ..	23	21·7	12	24·0	11	19·6

TABLE II.—*Incidence of Infection of the Upper Respiratory Tract at Clinical Onset of Hodgkin's Disease*

Month	No. Presenting with Hodgkin's Disease	With Upper Respiratory Infection	
		No.	%
January	14	1	7·1
February	6	1	16·7
May	7	1	14·3
June	7	2	28·5
August	6	1	16·7
December	23	5	21·8

TABLE III.—*Management of Patients in First Six Months*

	No. of Patients
Local radiotherapy (also surgery in 3)	40
Local and "prophylactic" regional radiotherapy ..	10
Local radiotherapy and chemotherapy	8
Local radiotherapy and "prophylactic" regional radiotherapy and chemotherapy	3
Chemotherapy only	5
Surgery only	2
Treated more than six months after onset	38

Discussion

No observations on a seasonal incidence of Hodgkin's disease have been recorded in the literature so far reviewed.

Hodgkin's disease is rare and few new patients are seen each year at any one centre. The present analysis has been made on 269 patients with histologically proved Hodgkin's disease who attended one hospital in the 15 years 1945 to 1959. In 106 of these the disease began with the enlargement of a superficial lymph node and remained localized for at least six months. In 23 (21.7%) the clinical onset of the disease occurred in the month of December. The same monthly incidence throughout the year was also found in the nine years 1945–53, and in the six years 1954–9.

A series of cases such as this cannot be regarded as unselected. For the purpose of the analysis, patients with superficial and localized disease initially have been deliberately chosen. Nevertheless, there is no obvious feature in the group to suggest that it is unrepresentative of Hodgkin's disease. The ratio of males to females is 2:1 for the whole group of 269 and for the selected 106 patients. Among these 106 patients the seasonal incidence is essentially the same for both sexes. The age distribution is also the same in each group for both males and females, with males presenting at a rather younger age. The subsequent course of the illness in the selected group has been typical of Hodgkin's disease, with no features to distinguish it from the course in the 163 patients excluded from the series.

One obvious explanation for a seasonal presentation is that the attention of patients would be drawn to

previously unrecognized enlarged nodes by a coincidental infection of the upper respiratory tract. More patients with Hodgkin's disease would be likely to present when these infections are commonest—namely, the winter months. It was therefore of particular interest to find that only 10.4% of all the patients presented with coincidental or recent upper respiratory infection and that these were not most prevalent in the month of the highest incidence of Hodgkin's disease. It is concluded that the high incidence of Hodgkin's disease in December was independent of the incidence of infection of the upper respiratory tract.

Some infections characteristically show a seasonal incidence. It would be of interest to compare with Table I the monthly prevalence of known infective agents. If, in fact, the pattern of seasonal occurrence of Hodgkin's disease is confirmed, it might support the view that Hodgkin's disease is caused by an infective agent or that its onset is precipitated by such an agent.

Summary

Of 106 cases of localized Hodgkin's disease in the period 1945–1959, 23 (21.7%) had a clinical onset in the month of December.

The same seasonal incidence is seen in the two groups of 50 and 56 patients whose disease commenced in the periods 1945–1954 and 1955–1959 respectively.

The same pattern of seasonal occurrence is observed in both sexes.

The occurrence of upper respiratory tract infection in 11 patients did not lead to the discovery of lymphadenopathy nor was the relative incidence of sore throat greater in the month of December.

Since recurrent Hodgkin's disease so frequently involves deep-seated nodes, the inception of recurrence is impossible to establish. Peripheral node recurrence in 89 cases showed no striking seasonal incidence.

No particular seasonal incidence of onset was found in a series of 48 cases of lymphosarcoma and reticulosarcoma.

No explanation is offered for the seasonal incidence observed, but the results might support the view that Hodgkin's disease is caused by an infective agent or that its onset is precipitated by such an agent.

These results are presented in the hope that comparable studies will be made elsewhere.

This work was supported by a grant from the New South Wales State Cancer Council, Australia, and in part by a Gordon Jacobs Fellowship, The Royal Marsden Hospital, London. Thanks are extended to Dr. D. A. G. Galton for his help in the preparation of this paper, and to Professor A. Haddow, Professor D. W. Smithers, Dr. Eve Wiltshaw, and Dr. R. A. M. Case for their helpful comments.

A new British Standard (B.S. 3385) for dosimeters lays down requirements for direct-reading personal dosimeters for *x*- and gamma-radiation. These instruments—a common type of which looks like a fountain-pen—fit into the pocket. They tell the user the amount of radiation dose he has received, if any. Obviously, it is essential that these instruments should be robust and accurate, and the requirements of B.S. 3385 are intended to ensure that they are. It is the first British Standard to be prepared under the authority of the newly formed Nuclear Energy Industry Standards Committee of the British Standards Institution. Copies may be obtained from the Institution, Sales Branch, 2 Park Street, London W.1, price 3s. each, postage extra to non-subscribers.

D

Preliminary Communications

Intrasplenic Isotopes in Study of Portal Systemic Collateral Circulation

Investigations of the portal systemic collateral channels in patients suffering from portal hypertension have been almost restricted to the visualization of these channels, chiefly by portal venography, and by the demonstration of varices at the lower end of the oesophagus radiologically with barium. These procedures, though of value in many cases in outlining the collateral channels, do not satisfactorily reveal the true size of the "shunt" through which blood is diverted from the portal to the systemic circulation. More accurate assessment of this shunt would be of value, particularly before deciding on the surgical treatment to be followed, and postoperatively for checking the results of the various anastomotic procedures performed.

Percutaneous intrasplenic injection of radioactive materials appears to offer a method for the evaluation of the circulatory dynamics of the portal circulation and its collateral channels with the systemic circulation. The results in three normal subjects and 11 patients with portal hypertension are given.

Materials and Methods

Two identical Ekco scintillation probes, type N 559 D, attached to a low-angle collimator, are used. One probe is placed over the liver laterally and the other over the right side of the heart (Fig. 1). Both probes are adjusted so as to be in close contact with the patient's skin. The probes are connected to Ekco scalers, which record the time in seconds against a pre-set count.

Different types of radioactive isotopes were used—namely, colloidal 198Au, ^{131}I-labelled human serum albumin, and ^{131}I-labelled rose Bengal. The latter, with a short biological half-life, seems to be most satisfactory (Fellinger *et al.*, 1958 ; Baptista and Carvalho, (1958).

With a thin lumbar-puncture needle the spleen is punctured in the eight, ninth, or tenth intercostal space in the mid-axillary line. With very large spleens a subcostal approach is used. After recording the splenic pressure by means of a saline heparinized manometer,

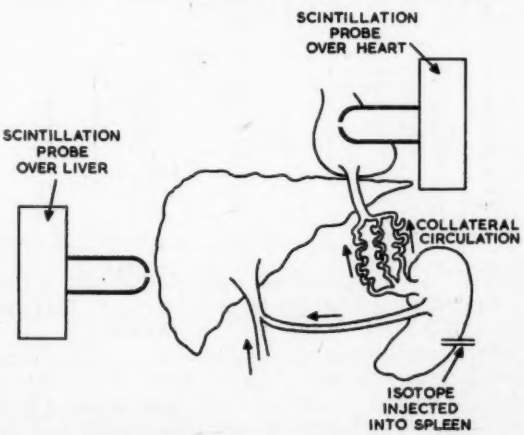

FIG. 1.—Diagram illustrating the method used for tracing the radioisotope injected into the spleen in a case of portal hypertension with a marked portal systemic circulation.

25 μc of the tracer material contained in 0.5 ml. of sterile isotonic saline is rapidly injected into the spleen, and the counters are simultaneously started. The time in seconds (for a pre-set count) is repeatedly recorded until constant readings are obtained. Five successive readings are then registered to obtain two lines for heart and liver.

Clinical Studies.—All the patients with portal hypertension chosen suffered from bilharzial liver fibrosis, which is the commonest form of liver cirrhosis in Egypt (Erfan, 1947). The pathogenesis of this condition is dependent on the deposition of bilharzial ova in the portal tracts. This is followed by periportal fibrosis and constriction of the intrahepatic branches of the portal vein. The liver parenchyma itself is affected only later in the course of the disease. The size of the spleen, enlarged in all cases, is not an index of the degree of portal hypertension present since it is affected by other factors. Cases 6, 9, and 11 had a moderate degree of ascites. Case 4 had severe ascites. All cases showed a variable degree of undernutrition, anaemia, and hypovitaminosis. The three normal subjects chosen showed no evidence of liver cirrhosis or enlarged spleen, and were regarded as controls.

RESULTS AND DISCUSSION

The time is calculated in seconds from the moment of injection of the tracer dose until the saturation point is reached over both the liver and the right side of the heart. The saturation point is taken as the point at which constant readings are obtained. The results are shown in the accompanying Table. The time taken for the saturation point to be reached over the heart varied from 1.6 to 9.5 seconds in patients with portal hypertension. In control normal subjects this varied from 22.7 to 27.6 seconds. The corresponding time over the liver in patients with portal hypertension varied from 6 to 14.9 seconds, whereas in control normal subjects it varied from 3 to 3.9 seconds. The results obtained from one normal subject (Case 1) and from one patient with portal hypertension (Case 7) are represented by two

Case No.	Age and Sex	Size of Spleen (in Fingers)	Splenic Pressure (mm. Saline)	Saturation Point (Time in Seconds)	
				Liver	Heart
Normal Subjects					
1	25 M	—	120	3·2	25
2	40 M	—	100	3·9	27·6
3	30 F	—	90	3	22·7
Patients with Portal Hypertension					
4	55 M	3	250	8	No
5	15 M	4	340	11	4·5
6	45 F	5	340	14·9	8·5
7	30 M	2	290	9·3	2·5
8	30 M	3	200	6	7·7
9	35 F	4	410	No	9·5
10	25 F	2	190	14	7·2
11	22 M	5	520	12	3·4
12	34 M	2	180	14·1	1·6
13	30 M	2	160	12·6	6·8
14	32 M	6	390	No	2·5

No=Could not be determined.

curves on semilogarithmic paper (Fig. 2). The saturation point could not be determined over the liver in Cases 9 and 14 or over the heart in Case 4.

These quantitative differences between normal subjects and patients with portal hypertension seem to depend directly on the patency and the size of the portal systemic collateral channels, and may provide a fairly practical and easy method for assessing the size of these channels.

The results seem to bear a relationship to the degree of splenic pressure. In general, the higher the splenic pressure obtained, the sooner the saturation point is reached over the heart and the slower it is reached over the liver.

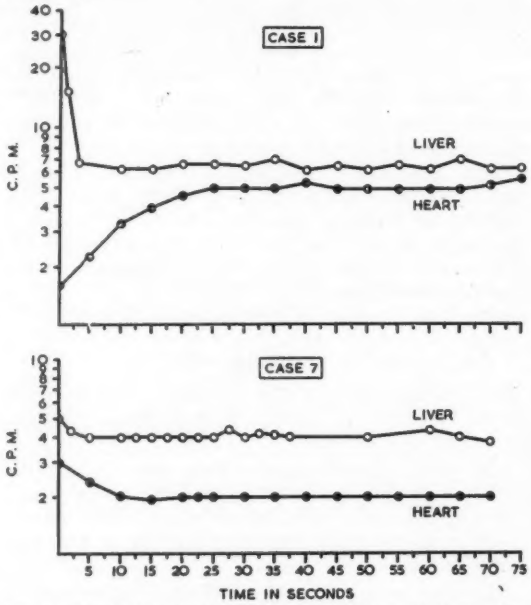

FIG. 2.—Time taken for saturation point to be reached over the liver and the heart is shown in a normal control subject (Case 1) and in a patient with portal hypertension (Case 7). C.P.M.= Count per minute.

Other factors may modify the results. Thus a large spleen may give rise to stagnation or dilution of the radioactive material. Differences may also be obtained, depending on the site of the tip of the needle in the splenic pulp or in the larger venous branches of the splenic vein. Thrombosis of the splenic vein would also presumably greatly modify the results. This should be detected by splenic venography. An ideal method would make use of a material which is both radio-opaque to visualize the portal tracts and to study their circulatory dynamics' (R. H. Greenlaw and S. I. Schwartz, 1961, personal communication).

The results suggest that patients with short times over the heart have a larger portal systemic collateral circulation. More elaborate timing, however, is necessary, using rate-meters and quick chart recordings, for developing an accurate quantitative method of assessing the shunt.

The technique described may also be helpful in the investigation of obscure cases of splenomegaly and in the differential diagnosis of haematemesis due to bleeding varices.

SUMMARY

A method is described using percutaneous intrasplenic injection of isotopes to study the dyamics of the portal systemic collateral circulation.

Results obtained from 11 patients with portal hypertension are compared with those obtained in three normal subjects.

The quantitative difference between normal persons and patients with portal hypertension apparently depends directly on the patency and size of the portal systemic collateral channels.

The factors which may alter the results obtained are discussed.

We are grateful to Dr. M. Bender, Director of the Department of Radioisotope Research, Roswell Park Memorial Institute, New York, for his invaluable collaboration during this study. Our thanks are also due to M. Badr Eldin, Y. E. Megahed, and H. T. H. Soliman for their assistance.

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Medical Memoranda

Pancreatic Cyst in Infancy: Recovery after Marsupialization

Pancreatic cyst is a very rare condition: Aldis, quoted by Aird (1957), found only 2 in 75,000 patients. Most cysts have occurred in adult females. The condition is exceedingly rare in childhood and infancy. Miles (1959), in a review of the literature, found only eight cases in infants under 2 years of age, and, of these, cysts were demonstrated at birth in only two, and none was operated upon in the neonatal period. His own case was that of a full-term female baby who was operated upon when 8 days old. There had been frequent regurgitation of the baby's feeds with increasing abdominal distension. Examination of the abdomen and chest by *x* rays, intravenous pyelogram, barium meal, and barium enema showed a homogeneous shadow over most of the abdomen, with upward and medial displacement of the stomach and downward displacement of the large and small intestines. Laparotomy revealed a large thin-walled multilocular cyst arising from the head and body of the pancreas: the cyst was excised and the baby made a satisfactory recovery.

CASE REPORT

The patient, a full-term first-born male child, was seen in the Waterford Maternity Hospital when 23 days old. He had been admitted with a history of intermittent vomiting since birth. The child was healthy-looking when first seen and weighed 7 lb. (3.2 kg.). Abdominal examination revealed a firm round swelling the size of a grapefruit in the hypogastrium: it could be freely moved over the greater part of the abdomen.

Operation was performed on the same day, the abdomen being opened through a supraumbilical midline incision. The cyst was seen to present between the stomach and the transverse colon. The gastrocolic omentum was incised and the cyst exposed. It was fairly thin-walled and was seen to arise from the neck and adjacent portion of the body of the pancreas. The cyst could easily be separated from the stomach and colon but was intimately blended with the pancreas over a distance of several centimetres. The splenic vessels were closely attached to the base of the cyst. It was decided not to attempt complete extirpation. The fluid was removed as completely as possible by aspiration, after which the greater part of the cyst wall was excised. The margin of the remaining portion of the cyst was then sutured to the peritoneum of the middle third of the abdominal incision, using No. 1 chromic gut. The linea alba and the skin in the remainder of the incision were repaired with interrupted nylon sutures.

Over the course of the next 12 hours 120 ml. of half-normal saline, with added hyalase, was given subcutaneously, and 24 hours after the operation oral feeding with half-strength expressed breast milk was begun. Streptomycin 0.25 g. and penicillin 250,000 units were given twice daily for eight days. The child vomited approximately half of each feed on the day after operation and vomited once on the second post-operative day, otherwise the post-operative course was uneventful. Drainage from the wound continued for over two months after the operation. During this time the child's general condition was satisfactory in every respect. A tendency to excoriation of the edges of the wound was immediately checked by the use of I.C.I. barrier cream. On January 4, 1960, the wound dressing was completely dry for the first time, and on January 7 the wound was healed and remained so. On January 23 the baby's weight was 12 lb. 4 oz. (5.6 kg.) and he was taking full milk, "farex," rusks, and egg yolks. No swelling could be felt on abdominal palpation.

On May 6, over six months after the operation, the mother stated that he seemed to be healthy in every way, that he was feeding satisfactorily, and that his bowels were regular with normal-coloured stools. On examination he looked very well. The wound was soundly healed and no abnormality was found on palpation of the abdomen. His weight was 19 lb. 7½ oz. (8.8 kg.). In December Dr. Evelyn S. Harris, of Seattle, Washington, kindly sent me a report on the patient: he was well in every way and weighed 24 lb. 7½ oz. (11.1 kg.).

Microscopical examination of the cyst wall showed that it consisted of fibrous tissue lined by a very flattened epithelium. Diastase could not be demonstrated in the fluid; trypsin was present to a titre of 1/40.

COMMENT

More than one classification of cysts of the pancreas has been proposed. McPherson and Heersma (1948) classify pancreatic cysts as follows: (1) retention cysts; (2) proliferation cysts (tumour); (3) congenital cystic disease; (4) parasitic cysts; (5) pseudocysts; and (6) dermoid cysts. Fibrocystic disease of the pancreas is not usually characterized by gross cyst formation. In the present case the origin of the cyst from the pancreas could be clearly demonstrated at operation: one can only speculate on whether the cyst was a true cyst or a so-called pseudocyst. Pseudocysts arise as a result of previous inflammation or injury, and there was no evidence that either of these had occurred in post-natal life, and presumably the opportunities for the occurrence of either condition in antenatal life are limited.

The case described here showed no external evidence of congenital abnormality, and, with one exception, this is in accordance with the cases traced in the literature. The exception is the case described by de Lange and Janssen (1948). Necropsy showed a cyst about the size of a grapefruit lying below the stomach and liver. The right foot showed six toes, the right lung had only two lobes, and there was marked enlargement of the cisterna magna.

In most of the reported cases in childhood and in adult life abdominal distension has been evident and abdominal palpation has shown this to be due to the presence of a swelling in the upper part or left side of the abdomen. Vomiting has been a cardinal symptom in the cases occurring in childhood and infancy. In the adult the swelling is usually central and fixed. In the above case the cyst at the first examination was

in the site usually occupied by a distended urinary bladder, and on being moved manually from its position it slipped upwards to lie above the umbilicus and tended to remain there. Its extreme mobility was presumably attributable to a mobility of the retroperitoneal structures as a whole, since the cyst did not possess a long pedicle but was attached to the pancreas by a short and broad base.

In the reported cases the investigations carried out have included "straight" *x*-ray film of the abdomen, *x*-ray film of chest, barium meal, barium enema, and intravenous pyelogram. The necessity for these procedures, involving considerable exposure of the infant to radiation, is doubtful, since vomiting in infancy which persists in spite of conservative measures raises the question of surgical exploration, which is put beyond doubt by the finding of an abdominal tumour. There is unlikely to be any difficulty in distinguishing the tumour from the "tumour" of hypertrophic pyloric stenosis.

There is no general agreement on the form surgical treatment should take, though it is commonly stated that excision of the cyst is the ideal treatment but that it is not always feasible owing to close adhesion to surrounding structures. Where excision is regarded as impracticable, the choice of treatment lies between marsupialization and anastomosis of the cyst to the stomach, duodenum, or jejunum. In the present case it was felt that complex excision should not be attempted and that the wall of the cyst was so thin as to render an anastomosis with any part of the gastro-intestinal tract unsafe. Marsupialization, a less extensive procedure than either excision or anastomosis, was therefore carried out with satisfactory results.

I am indebted to Dr. K. Cuddihy, Kilkenny, for the examination of the cyst wall and fluid.

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Idiopathic Myoglobinuria

Idiopathic myoglobinuria is a rare disease in which myoglobin is liberated from muscle tissue and excreted by the kidney. We encountered an example of this condition in a previously healthy young man, and have investigated methods for the detection of the urine pigments.

CASE REPORT

The patient, a youth of 19, had always led a sedentary existence; on the afternoon of September 27, 1959, he played football for the first time for two years. During the game he sustained a kick on the left thigh which, although it did not prevent his finishing the game, left a small bruise. Later that evening he noticed pain and stiffness in the muscles of the lower back and thighs, and weakness of both legs. The pain prevented sleep that night, and by the next morning the weakness of the legs and back had increased to an alarming extent, so that he was not able to sit up unaided in bed. He then noticed for the first time that his urine was dark red in colour.

He was admitted to hospital 18 hours after the onset of symptoms. His general condition was satisfactory, temperature, pulse, and blood-pressure being normal. Because of profound weakness of the extensor muscles of the back and thighs he was unable to lift himself unaided from the supine to the sitting position, or to raise either leg off the bed. Although the muscles of both thighs were tender on palpation, there was no swelling of the affected muscle groups. Knee reflexes, although diminished, were equal. There was no abnormality of other muscle groups, and examination of other systems revealed nothing abnormal.

Investigations.—The urine passed on admission—that is, 24 hours after the game of football—contained no albumin, sugar, red blood cells, or casts, but was port wine in colour, and contained myoglobin and metmyoglobin. The blood count, serum bilirubin, liver-function tests, and electrolytes were normal, and no excess urinary porphyrins were detected. The plasma creatine and creatinine were normal, but the excretion in the urine showed characteristic changes:

Urine creatinine	1.8 g./litre	24 hours after onset of symptoms
„ creatine	0.2 g./litre	
Urine creatinine	0.7 g./litre	36 hours after onset of symptoms
„ creatine	0.2 g./litre	

Muscle biopsy from an affected muscle group in the thigh, performed five days after admission to hospital, showed normal voluntary muscle, with no evidence of breakdown of fibres or loss of striation (Dr. K. A. D. Turk).

After admission there was a steady improvement with return of power to the affected muscles; within 24 hours there was no detectable weakness or muscle tenderness, and the knee reflexes had returned to normal. Urine passed on the morning after admission still contained myoglobin although only in about one-twentieth of the concentration in the first specimen. At no time during the illness did he develop oliguria or urea retention.

This type of episode had never occurred previously in the patient or other members of his family. The youth had never been very energetic or taken strenuous exercise. He subsequently admitted to having had similar pain in the back and thighs, and slight weakness of the legs, lasting 24 hours, on two previous occasions, both associated with an infection of the upper respiratory tract. He had not noticed any alteration in the colour of the urine during these episodes.

IDENTIFICATION OF MYOGLOBIN

The identification of the urine pigment is usually made spectroscopically, although Whisnant, Owings, Cantrell, and Cooper (1959) used the ultracentrifuge and paper electrophoresis. The latter test takes several hours and it is advisable to have an authentic sample of human myoglobin for comparison. Both haemoglobin (Hb) and myoglobin (Mb) are rapidly oxidized in urine to their met-derivatives, the spectral characteristics of which are not very different. Direct examination of the urine may therefore show, as in this case, both MbO_2 and metMb, which may not be easy to identify. Berenbaum, Birch, and Moreland (1955) showed that the absorption maxima of HbCO and MbCO were sufficiently separated to permit this method to be used to identify the pigment present in the urine of their case. The spectra of a number of derivatives were therefore compared to see which would provide the best distinction between Hb and Mb.

A Hb solution was used as a control, and absorption spectra were measured with Unicam SP 500 spectrophotometer. The absorption maxima found, and those previously reported, are given in the Table.

The acid met-derivatives (urine, buffered to *p*H 6, plus 2 drops dil. $K_3Fe(CN)_6$) did not give sharp maxima in the visible region of the spectrum, possibly because of "background" absorption by other urine pigments. These spectra would be of little use as a diagnostic test, although the Soret bands (406 and 410 mμ) were clearer. The absorption spectra of the met-cyanide derivatives

(prepared by adding 1 drop NaCN to the acid met- solutions) were virtually identical, except for the Soret region, where maxima again showed a definite shift in wavelength. The reduced compounds (sodium dithionite in the absence of air) also showed significant shifts in the Soret bands. The oxy-derivatives were prepared by reduction with sodium dithionite, followed by oxidation by shaking with air for several minutes. These were not very stable, but the spectral differences (Fig. 1) are easily seen. The carboxy-compounds were prepared by bubbling coal-gas through the solution for several minutes before and after adding a little sodium dithionite, and then covering the solution with a layer of liquid paraffin. These derivatives were relatively stable, with clear differences in spectra (Figs. 2 and 3).

Absorption Maxima of Hb and Mb Derivatives. The Hb Maxima are Taken from Lemberg and Legge (1949) and Those for Mb from Smith and Gibson (1959). The Values Found in this Case are Shown in Parentheses

Compound	Absorption Maxima		Shift of Mb band (mμ)
	Hb (mμ)	Mb (mμ)	
Acid met- ..	630 (630) 500 (496) 405–407 (406)	630 (640) 500 (494) 407–408 (410)	0 (+10) 0 (−2) 0 to +3 (+4)
Met-cyanide ..	540 (540) 412–416 (420)	540 (540) 422 (422)	0 (0) +6 to +10 (+2)
Reduced- ..	555 (556) 430 (430)	552–555 (556) 432–435 (433)	0 ,, −3 (0) +2 ,, +5 (+6)
Oxy-	576–578 (576) 540–542 (542) 412–415 (413)	582 (580) 544 (548) 418–420 (420)	+4 ,, +6 (+4) +2 ,, +4 (+6) +3 ,, +7 (+7)
Carboxy- ..	568–572 (568) 538–540 (538) 418 (419)	580 (578) 540–542 (542) 422–424 (423)	+8 ,, +12 (+10) 0 ,, +4 (+4) +4 ,, +6 (+4)

The absorption maxima of the Mb derivatives were nearly all at higher wavelengths than those of Hb. The absorption minima of the oxy-compounds (HbO_2, 560 mμ; MbO_2, 568 mμ) and carboxy-compounds (HbCO, 554 mμ; MbCO, 560 mμ) were also displaced in the same direction. If the spectrophotometer is used, with either the oxy- or carboxy-derivatives, these spectral differences provide a reliable means for the identification of the pigment, and by using the Soret bands the method may be rendered more sensitive.

COMMENT

The diagnosis before admission to hospital was haematuria secondary to renal injury. When this was disproved by examination of the urine deposit other possibilities considered were March haemoglobinuria, porphyria, and myoglobinuria. The differentiation between these pigments is impossible by the naked eye, but may be made spectroscopically, as described above.

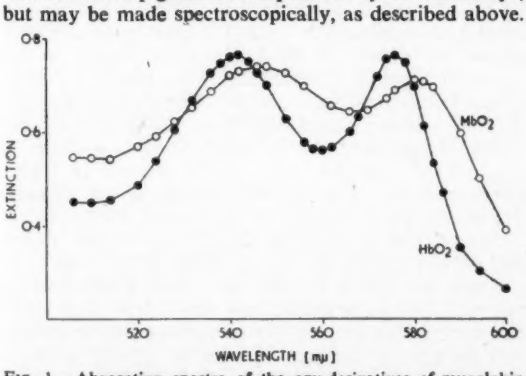

FIG. 1.—Absorption spectra of the oxy-derivatives of myoglobin (MbO_2, —○—○—) and haemoglobin (HbO_2, —●—●—).

Myoglobin, a haem-pigment present in red muscle, is excreted in the urine after breakdown of muscle tissue. This may occur secondary to injury to voluntary muscle, as in the crush syndrome, or to primary muscular disease, such as dermatomyositis or muscular dystrophy (Acheson and McAlpine, 1953), or consequent to the ingestion of some toxic agent, as in Haff disease.

In primary idiopathic myoglobinuria there is no known primary muscular disease. Muscle pain, cramps, or paralysis may occur temporarily, but these are probably due to the breakdown of muscle cells, liberating myoglobin. There are fewer than 20 cases of this type in the literature (Elek and Anderson, 1953; Berenbaum *et al.*, 1955; Whisnant *et al.*, 1959). We consider our case to be of this type. The symptoms did not develop until several hours after the game of football, and the amount of primary muscular trauma was minimal, and could in no way be compared with the secondary myoglobinuria of the crush syndrome. The relatively trivial course of the illness suggested that there was only a minor degree of muscle breakdown, and this may explain the absence of any histological change, such as that described by Berenbaum *et al.* (1955).

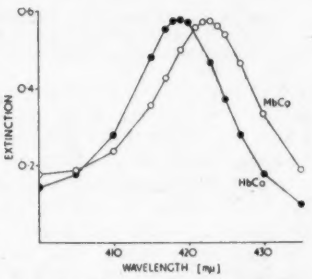

FIG. 2.—Absorption spectra of the Soret bands of the carboxy-derivatives of myoglobin (MbCO, —○—○—) and haemoglobin (HbCO, —●—●—).

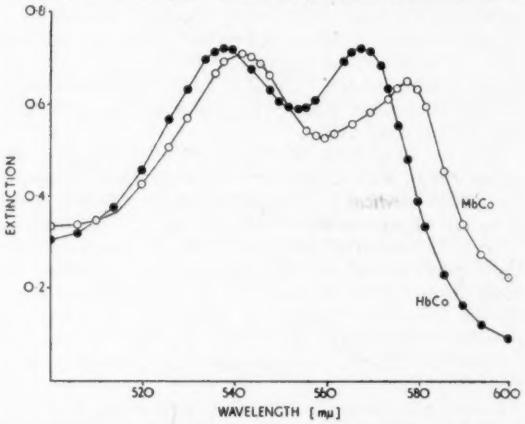

FIG. 3.—Absorption spectra of the carboxy-derivatives of myoglobin (MbCO, —○—○—) and haemoglobin (HbCO, —●—●—).

We thank Dr. M. Hamilton for permission to publish this case, and for advice in the preparation of this paper.

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Reviews

GUIDE TO THE MAZE

Drugs in the Treatment of Disease. The British Medical Journal. Foreword by Hugh Clegg, Editor *B.M.J.* (Pp. 516 +x; illustrated. 35s.) London: British Medical Association. 1961.

Voltaire defined medical treatment as the art of pouring drugs of which one knew nothing into a patient of whom one knew less, and for over 200 years after Voltaire's death his cynicism was very nearly true: for anatomy, physiology, pathology, and diagnostic medicine had to blaze the trail along which therapeutics could eventually advance, and it has really only been during the last thirty years that medical therapeutics has deserved the name of a science. Nevertheless, during that time its advance has been so outstandingly rapid that it is very difficult to keep up with it, and there is no saying what the splendour and majesty of its progress will be in the next thirty years. Perhaps we will even be able to prevent the common cold. The advance has been, of course, most spectacular in drug therapy, and, largely owing to the ingenuity of the pharmaceutical manufacturers, the number of new drugs has increased to a bewildering extent.

In order to help the practising doctor to compare the newer drugs with each other and with older remedies the *British Medical Journal* published from 1958 to 1960 a series of authoritative articles under the heading "Drug Treatment of Disease." The articles have now been fully revised by their authors and published in book form. It is an excellent work and covers most of the common therapeutic problems of everyday practice. The authors have obviously been chosen with scrupulous care and have succeeded in condensing into their short chapters a mass of practical, up-to-date, and accurate information. Nevertheless, it is an easy and pleasant book to read and can be dipped into with great profit by anyone in active practice, be he specialist or practitioner. The benefits to be derived from reading it are out of all proportion to the modest price of the volume.

DERRICK DUNLOP.

NARCOSIS IN THE U.S.S.R.

Sleep Therapy in the Neuroses. By B. V. Andreev, M.D. Translated from Russian by Basil Haigh, M.A., M.B., B.Chir. (Pp. 114. $8.50.) New York: Consultants Bureau.

This monograph is of interest not only for its subject matter but also for the glimpse it affords of current theory and practice in Soviet psychiatry. The rationale of sleep therapy is based on Pavlov's view of the neuroses as a state of partial nervous inhibition which is a protective mechanism preventing excessive demands on the cerebral cortex in the face of overwhelming stress. It is claimed that sleep therapy, by increasing the degree of inhibition, allows the restoration of exhausted nerve cells and enables other forms of treatment to act.

The author begins by elaborating Pavlov's theories and then describes recent Soviet experience with sleep therapy in the neuroses and some psychoses, especially catatonic schizophrenia. He reviews the relevant Soviet literature, some of which is quite critical—for example, we learn that some experimental neuroses in animals were aggravated by sleep therapy. The best results are obtained in neurasthenia, anxiety with phobias, and psychogenic visceral disturbances such as hypertension and peptic ulcer. Hysteria is more resistant but writers' cramp responds well. Obsessional states and hypochondriasis usually show no response. The author then describes his technique of determining the duration of sleep by the automatic recording of the patients' motor activity and provides illustrative records and a diagram of the apparatus. He goes on to present his own results in 91 patients with neurasthenia or hysteria who were treated with small doses of barbiturates to provide two four-hour periods of sleep during the day and 10 hours at night for one to three weeks. Hypnosis and direct suggestion were also used, and placebos were sometimes effective after several days on barbiturates. Of the patients 17% were cured and 36% considerably improved; only 3.5% showed no improvement at all. These observations are uncontrolled, but the author seems to be aware of this since he emphasizes that sleep therapy is no panacea but is a stage of treatment in preparation for other forms of therapy. Those with experience of our essentially similar technique of prolonged narcosis will no doubt agree. The author presents his case with moderation and discrimination and there are some indications that an empirical attitude may be developing within the Pavlovian framework of Soviet psychiatry.

The translator has contrived to present a rather difficult thesis in readable form, and a fairly extensive bibliography of Soviet and Western literature is provided.

K. DAVISON.

EXPERIMENTAL PSYCHIATRY IN U.S.A.

Lectures on Experimental Psychiatry. Pittsburgh Bicentennial Conference, Western Psychiatric Institute and Clinic, March 5–7, 1959. Editor: Henry W. Brosin, M.D. (Pp. 361+vi. $7.50.) Pittsburgh: University of Pittsburgh Press. 1961.

This book contains 17 chapters based upon contributions to a conference on experimental psychiatry held in Pittsburgh in 1959. The majority of the contributors are psychiatrists and—as can be expected in the U.S.A. —most of these are also psycho-analysts. It is, however, typical of the balanced approach of the Western Psychiatric Institute that Dr. H. W. Brosin, its director, can write in his preface to this volume: "Psychiatry and medicine are rooted in the biological and social sciences." The wide range of contributors to this volume indicates that he does not merely pay lip-service to psychiatry's parent disciplines.

One can read here a number of highly stimulating papers, rich in both factual and imaginative material. A few of these are research reports. The chapters by the experimental psychologists, R. A. Patton ("Hemicerebrectomy and Adaptive Behaviour in the Rhesus Monkey") and E. R. Hilgard ("Hypnosis and Experimental Psychodynamics"), are the most specific in their choice of theme, whereas Howard Liddell, in his "Contributions of Conditioning in the Sheep and Goat to an Understanding of Stress, Anxiety and Illness," gives a valuable résumé of many years' research on animal behaviour. A. S. Marrazzi also provides a survey of studies and techniques of research in neuropharmacology. A particularly comprehensive chapter, one which can be strongly recommended as background reading for its topic, is Joel Elkes's review of the history and development of studies of psychotropic drugs.

There are also a number of "think pieces" which contain less factual matter, but which provide, in brief compass, rather striking illustrations of the viewpoints and attitudes to research of men so various as Franz Alexander, Warren McCullough, R. L. Birdwhistell (who

has created a system of notation for non-verbal modes of communication), Lawrence Kubie, and Robert H. Felix, the public-health-minded director of the National Institute of Mental Health. This does not exhaust the list of contributors, but it will perhaps suffice to indicate that this volume deserves a place in the library of any hospital where registrars are working for their D.P.M. or where consultants are interested in keeping abreast with current thinking in psychiatric research.

G. M. CARSTAIRS.

RENAL DISEASE SYMPOSIUM

Recent Advances in Renal Disease. The Proceedings of a Conference held in London at the Royal College of Physicians of London, July 22–23, 1960. Edited by M. D. Milne. (Pp. 254+ix ; illustrated. 25s.) London: Pitman Medical Publishing Co. Ltd. 1960.

The publication of the proceedings of conferences is frequently condemned, and not without reason, but it can be valuable, as the present book shows. The material is likely to be fresh and up to date. It is easier for the organizers of a conference to ensure that papers are not repetitive or contradictory than for the editor of a book, and the limitation of time of speaking and the criticism of the papers before publication impose sanctions on egotistical contributors. Records of discussion can be tiresome when they come direct from the tape recorder and include social jocularities and irrelevances. Nevertheless, they can be as useful, by making the reader think, as the riders to a geometrical theorem or the conversation after a piece of foreign translation.

On all these counts this monograph scores high. It has been quickly and cheaply produced, and gives a readable account of renal function and structure, acute renal failure, metabolic aspects of renal disease, and the renal aspects of hypertension. There is much of interest to those who are not professional nephrologists. Renal amyloidosis, which is now much the commonest manifestation of amyloidosis, can be diagnosed with assurance only by renal biopsy. The prognosis of the nephrotic syndrome has been improved by better diuretic agents, but there is sufficient doubt about the long-term effects of corticosteroids to justify a controlled therapeutic trial. The life history of acute and chronic pyelitis and pyelonephritis, embracing all forms of the disease, remains to be written. There is more that one could comment on, but one must close by congratulating the Royal College of Physicians and Professor M. D. Milne on an excellent monograph.

L. J. WITTS.

CARE OF PHYSICALLY HANDICAPPED CHILDREN

The Care of Invalid and Crippled Children. Edited by A. White Franklin, M.B., F.R.C.P. With a Foreword by Letitia Fairfield, C.B.E., M.D., D.P.H. (Pp. 158+xiii. 8s. 6d.) London, New York, Toronto: Oxford University Press. 1960.

This book, like its predecessor of 1938, has been issued by the Invalid Children's Aid Association and will prove helpful to social workers, almoners, health visitors, and to all those who are concerned with the care of physically handicapped children in hospitals, in schools, and in their own homes. It was prepared under the editorship of Dr. A. White Franklin, chairman of the Aid Association, and it contains sixteen chapters that describe the whole range of common physical handicaps, as well as some of the less common. Cerebral palsy, congenital heart deformity, epilepsy, bed-wetting, haemophilia, orthopaedic disabilities, and disorders of speech, hearing, and vision are some of the conditions covered ; while rarities such as phenylketonuria and galactosaemia also appear.

Sometimes the terminology is more suited to doctors and senior medical students rather than to social workers, but full marks must be given to the contributors—all recognized experts—for compressing so much valuable information into the small space of 158 pages. There is always a real need for this type of handbook ; if it is of small size and reasonable price, like this one, each worker can buy a copy and carry it about with her for easy reference. The absence of any diagrams or illustrations, probably on grounds of cost, is a disadvantage, because certain sections of the book—for example, those on congenital deformities of the heart and large vessels—could have been made clearer and therefore more interesting.

Dr. White Franklin concludes his preface with a reference to the important part social workers can play in helping parents and their handicapped children towards a fuller and more successful adjustment to the situation. To give this service the worker must know the medical and surgical background of her patients so that she can give general support to what the doctor has said, and emphasize his advice to the parents. But the most difficult and perhaps the most important part of her work centres upon the technique she uses, and this implies that, in addition to what she learns from this handbook, she should have a wide knowledge of human nature and the ability to explain, to encourage, and to comfort. Skill of this sort is born in a few people, but most need practical enlightenment to bring out their best ; and I suggest that in any future edition it would be useful to include a chapter on this topic. It would need to be written by a senior worker of long experience.

NORMAN B. CAPON.

NUTRITION REVIEWS

World Review of Nutrition and Dietetics. Volume 2. Edited by Geoffrey H. Bourne. (Pp 247+viii ; illustrated. 60s.) London: Pitman Medical Publishing Co. Ltd. 1961.

The title given to this series is perhaps rather misleading. No serious attempt seems to be made to present a balanced review of our knowledge of nutrition and dietetics throughout the world, beyond the inclusion of contributions on selected topics from authors in different countries. Moreover, the use of the word "dietetics" is deceptive—at least for the present volume, the second of the series, in view of the absence of any contributions written from the dietetic angle. Thus all the reviews deal mainly with experiments in the science of nutrition, and none with dietetics, defined as the detailed study and planning of the feeding of human subjects. Apart from these minor criticisms, however, the editor is to be congratulated on collecting together nine interesting articles and on combining them into a most attractive volume. Printing and the reproduction of the illustrations are excellent, and the chapters and headings are arranged with great consistency and clarity. A small fault, however, is the unnecessary waste of the reader's time by the omission of page numbers in the list of contributions in the front of the book.

A. Aschkenasy writes on proteins and haematopoiesis, including a section on the influence of hormones.

A well-illustrated article by D. S. McLaren describes the effect of malnutrition on the eye, with special reference to work with experimental animals. A. B. Eisenstein deals with dietary factors and adrenocortical hormone secretion, and covers interrelationships with ascorbic acid, pantothenic acid, vitamin B_6, sodium, and potassium. An excellent review by D. P. Cuthbertson and P. N. Hobson, on the microbiology of digestion, includes sections on the influence of antibiotics and on germ-free life. Therese Terroine summarizes experiments on the vitamin interrelationships of ascorbic acid, which may be beneficial, when given in large doses, to animals suffering from deficiency of several other nutrients. A valuable review on the role of carotene and vitamin A in animal feeding is contributed by W. A. McGillivray. The remaining three articles are concerned, directly or indirectly, with calcium metabolism. Thus A. D. Kenny writes on parathyroid glands and calcium metabolism, B. Englefeldt and S.-O. Hjertquist on vitamin D deficiency and bone and teeth structure, and T. Gordonoff and W. Minder on fluorine.

Two of the contributions have come from the United States, two from France, and one each from Sweden, South Africa, New Zealand, Switzerland, and the United Kingdom, a spread which, as the editor points out, "pretty well encircles the world." In regard to authorship, rather than subject matter, therefore, the title of the series does not call for criticism.

T. MOORE.

BRAVE ACCEPTANCE

The Watershed. By Reginald Payne. (Pp. 220. 18s.) London: Faber and Faber. 1961.

Mr. Payne has a memory so tenacious and precise that he can recall the sensations, and something more, of the liberation of consciousness from the matrix of a world to which, without much difference between them, his infancy adhered like a bud on its stem. Then, in a gradually enlarging freedom, his remarkable eye begins to select and appreciate the more engaging details of an environment that was as richly and as quaintly furnished—to an appreciative eye—as the chambers of an eccentric virtuoso. He grew up in a family dominated by love and a formidable crankiness. His father, who made mattresses and sold tables and chairs, was a talkative Unitarian, a devout vegetarian; when the young Payne went to a party, as he often did, he suffered torments of fear lest he be irretrievably corrupted by the forbidden flavour of a sausage roll.

He tells his story with a serene acceptance of the oddities which decorate so much of it. He has a grave and pleasant sense of fun, but he never makes fun of the parents who invited it, because the love which dominated their busy home had found in him a responsive love. He went to an extraordinary school in Clacton, and of it he might have made merciless fun; but he exposes its curious regimen without taking revenge for the indignities he suffered under it, and persuades his readers that the headmaster was a good man though some of his habits were ridiculous.

It is usually the malicious writer who has an exact and microscopic eye, but Mr. Payne shows us that charity can see with a more brilliant percipience; and this account of his early life reaches an appropriate end when he, a pacifist by nature and intellectual decision, becomes a medical orderly in a country hospital, and then a recruit in the Inns of Court O.T.C. His brave acceptance of an uncongenial discipline concludes a book that, delightful in its literary quality, is also conspicuous for the unusual mixture of generosity and insight that dictated it.

ERIC LINKLATER.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

A Guide to Cardiology. By J. C. Leonard, M.D.(Lond.), M.R.C.P.(Lond.), and E. G. Galea, M.B.(Queensland), M.R.C.P. (Lond.), M.R.A.C.P. (Pp. 267+xii; illustrated. 27s. 6d.) London and Edinburgh: E. and S. Livingstone, Ltd. 1961.

Fumifugium: or ***The Inconvenience of the Aer and Smoake of London Dissipated.*** By John Evelyn. Tercentenary edition. (Pp. 41; illustrated. 5s.) London: National Society for Clean Air. 1961.

Physiology for Nurses. By Deryck Taverner, M.B.E., M.D., F.R.C.P. (Pp. 236+ix; illustrated. 12s. 6d.) London: The English Universities Press Ltd. 1961.

A Brief History of the Hospital of Saint Bartholomew. By Gweneth Whitteridge, M.A., D.Phil., F.S.A., and Veronica Stokes, B.A. (Pp. 68; illustrated. No price.) London: The Governors of the Hospital of Saint Bartholomew. 1961.

Congenital Anomalies of the Face and Associated Structures. Proceedings of an International Symposium. Compiled and edited by Samuel Pruzansky, D.D.S. (Pp. 385+x; illustrated. £5 6s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications Ltd. 1961.

The Physiology of the Mouth. By G. Neil Jenkins, M.Sc. (L'pool), Ph.D.(Cantab.). Second edition. (Pp. 355+xi; illustrated. 40s.) Oxford: Blackwell Scientific Publications Ltd. 1961.

Virus and Rickettsial Diseases of Man. By Sir Samuel Bedson, F.R.S., M.D., D.Sc., F.R.C.P., A. W. Downie, F.R.S., D.Sc., M.D., F. O. MacCallum, B.Sc., M.D., M.R.C.P., and C. H. Stuart-Harris, M.D., F.R.C.P. Third edition. (Pp. 461+x; illustrated. 60s.) London: Edward Arnold (Publishers) Ltd. 1961.

Miscellaneous Notes. Twelfth Series. By F. Parkes Weber, M.D., F.R.C.P., F.S.A. (Pp. 7. 2s. 6d.) London: H. K. Lewis and Co. Ltd. 1961.

Problème der Ersten Lebenstage. 2. Düsseldorfer Symposium, 25 June, 1960. Edited by Professor Dr. Karl Klinke. (Pp. 147; illustrated. DM. 35.) Stuttgart: Friedrich-Karl Schattauer-Verlag. 1961.

The Serology of Conglutination and its Relation to Disease. By R. R. A. Coombs, M.R.C.V.S., B.Sc., Ph.D., Anne M. Coombs, B.A., Ph.D., and D. G. Ingram, D.V.M., M.V.S.C., Ph.D. (Pp. 210; illustrated. 40s.) Oxford: Blackwell Scientific Publications Ltd. 1961.

Roentgenology of Intracranial Meningiomas. By Sidney P. Traub, M.D. (Pp. 238+xxi; illustrated. £5 12s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications Ltd. 1961.

Genetics and Ophthalmology. By P. J. Waardenburg, M.D, A. Franceschetti, M.D., and D. Klein, M.D. (Pp. 992; illustrated. £13 10s.) Oxford: Blackwell Scientific Publications Ltd. 1961.

Africa and the Victorians. The Official Mind of Imperialism. By Ronald Robinson and John Gallagher, with Alice Denny. (Pp. 491+xii; illustrated. 45s.) London: Macmillan and Co. Ltd. New York: St. Martin's Press. 1961.

Physiologie Humaine. Cellulaire et Organique. By H. Laborit. (Pp. 585; illustrated. NF. 68.) Paris: Masson et Cie. 1961.

Functions of the Blood. Edited by R. G. Macfarlane, M.A., M.D., M.R.C.S., F.R.S., and A. H. T. Robb-Smith, M.A., M.D., F.R.C.P., M.R.C.S. (Pp. 635+liv; illustrated. £6.) Oxford: Blackwell Scientific Publications Ltd. 1961.

The Extra Pharmacopoeia (Martindale). Supplement to Volume I, twenty-fourth edition 1958, and Volume II, twenty-third edition 1955. Under the direction of the Council of the Pharmaceutical Society of Great Britain. (Pp. 315+xi. 32s. 6d.) London: The Pharmaceutical Press. 1961.

Manuel de Médicine. By Henri Péquignot. Second edition. (Pp. 709; illustrated. NF 53.) Paris: Masson et Cie. 1961.

BRITISH MEDICAL JOURNAL
LONDON
SATURDAY SEPTEMBER 2 1961

FLOUR BLEACHERS AND IMPROVERS

Wheat flour, even when freed from its coarse brown bran, has a faint yellow colour due to the presence of xanthophyll, a common plant pigment. It also has the property of forming a sticky, tenacious dough when mixed with water. For the production of a large white loaf of bread three things are necessary. First, the coarse fractions of the wheat grain, containing the bran, must be removed during milling. Secondly, the xanthophyll must be bleached, a process which involves its destruction by oxidation. Thirdly, the flour must be "matured" in order to produce dough of the right degree of tenacity. The tough dough then efficiently retains the small bubbles of carbon dioxide which are formed by yeast fermentation before baking, and expands well under their pressure during baking. When flour is stored in the presence of air oxidation diminishes its yellow colour, and increases the tenacity of the dough. The natural "maturing" or "improvement" of flour by ageing, however, demands the use of storage accommodation which would be excessively expensive under modern conditions. Dangers of pest infestation, moreover, would always be present, and the degree of oxidation attained would be very irregular.

For many years, therefore, chemical oxidizing agents have been used for the bleaching and improvement of flour. Critics of their use have always been apprehensive of their effects on public health, and in 1946 their fears were justified by the alarming observations of the late Sir Edward Mellanby.[1] He showed that flour treated with the improver nitrogen trichloride, or "agene," was associated with the development of hysteria in dogs. Though human volunteers failed to show injuries after the ingestion of agenized flour its use was obviously too dangerous to be allowed to continue.

The improving and bleaching agents which have replaced agene were recently reviewed in a report of the Food Standards Committee.[2,3] In the absence of a satisfactory method of flour improvement by aeration, or by physical means, the use of some chemical improver seemed unavoidable, in the opinion of the Committee, for the production of the kind of bread to which the public has become accustomed. The necessity for bleaching agents is more questionable, but prohibition of their use does not seem justifiable. No known flour additive other than agene, it may be emphasized, has a chemical structure which could give rise to the formation of methionine sulphoximine, the toxic agent which can cause hysteria in dogs. The report nevertheless recommended that only a short list of improving and bleaching agents for bread making and other purposes should be allowed. For bread making these are commercial chlorine dioxide (which contains some free chlorine), ascorbic acid, potassium bromate, and ammonium or potassium persulphate. Baking experts say that these improvers are self-limiting in that even slight excess over the usual commercial level causes the loaf to collapse during baking. The Committee saw no need, therefore, to set legal limits to the concentrations at which the improvers may be used.

The qualities in flour required for making cakes and biscuits are different from those required for making bread. For certain kinds of cakes the flour must be very heavily treated with chlorine, the concentration required being 900 p.p.m., or even more. This may be compared with 15 p.p.m. of chlorine dioxide generally necessary to improve flour for bread making. For biscuit making, flour is treated either by the miller with 20 p.p.m. of sulphur dioxide gas, or by the manufacturer by adding an equivalent quantity of sodium bisulphite. In view of the small proportions of the total flour consumption that are devoted to cakes and biscuits, the Committee considered that no control of the amounts of chlorine and sulphur dioxide used is necessary. The possibility that some people may eat much more cake than others, and so receive a substantial proportion of their flour intake in highly chlorinated form, seems to have been overlooked.

The Committee recommended that "all bleaching and improving agents in use should be subject to well-designed, long-term chronic toxicity studies." The treatment of flour with the substances tentatively permitted, which have already been mentioned, should be examined as further biological data become available, and in any case in three to five years' time.

An investigation by Mr. S. G. Impey and Dr. T. Moore on the effect of the treatment of flour with chlorine dioxide on the nutritive value of bread was reported in the *Journal* last week at page 553. When weanling rats of a single generation were given

[1] Mellanby, E., *Brit. med. J.*, 1946, **2**, 885.
[2] Food Standards Committee, *Report on Bread and Flour*, 1960, H.M.S.O.
[3] *Brit. med. J.*, 1960, **2**, 1659.
[4] Moran, T., Pace, J., and McDermott, E. E., *Nature* (*Lond.*), 1953, **171**, 103.
[5] Frazer, A. C., Hickman, J. R., Sammons, H. G., and Sharratt, M., *J. Sci. Food Agric.*, 1956, **7**, 375.
[6] Moore, T., Sharman, I. M., and Ward, R. J., ibid., 1957, **8**, 97.
[7] Stoner, H. B., *Nutritio et Dieta* (*Basel*), 1960, **2**, 1.

diets consisting mainly of bread no differences in growth rate were found between rats given bread made from untreated flour and those given flour treated with chlorine dioxide. But when the feeding trials were continued for several generations somewhat slower growth rates were observed in rats given bread made from treated flour than in others given bread made from untreated flour. The growth rates were graded according to the concentration of the improver used, being even slower when the flour had been heavily treated than when treatment was at about the usual commercial level. All the rats were given adequate weekly doses of vitamin E. The retardation in growth caused by treatment with chlorine dioxide did not therefore appear to be due to the destruction of this vitamin which is a well-established effect of the improver.[4–6] Moreover, when rats were allowed to choose between diets containing bread made from untreated flour and from treated flour, they generally preferred the latter. Their slow growth on bread made from treated flour, therefore, was not due to reduced palatability. An interesting point was that weights were lower at weaning in the young rats from mothers fed on treated flour than in those from mothers given untreated flour. Presumably the improver affected the growth of the rats not only while they were eating for themselves but also during gestation and lactation.

The increased volume and whiteness of the loaf promoted by chlorine dioxide, therefore, are obtained at the expense of one known defect in nutritive value, the destruction of vitamin E, and another unknown defect, indicated by the slow growth of rats in multi-generation experiments. In the face of this evidence of nutritional damage one may ask, Is it reasonable that the use of chlorine dioxide as a flour improver should be allowed to continue? Before attempting to answer this question we must first remember that the acceptance of slight loss in nutritive value as the price of increased digestibility and palatability is commonplace in domestic cooking and in food manufacture. Thus some vitamin E must be lost even when untreated flour is baked into bread; toasting must cause substantial losses in many nutrients. Next we must recognize that experiments with rats given bread as the main component of their diet may well be misleading if their results are to be applied to human subjects, who subsist mainly on foods other than bread. The loss of vitamin E from bread, for example, may seem unimportant when large amounts of this vitamin can be obtained in human diets from margarine and cooking fats, and when in any case opinions differ about the importance of vitamin E in human nutrition. On the balance of the evidence at present available, therefore, it seems reasonable, as short-term policy, that the use of chlorine dioxide should be continued.

When we take a longer view, however, doubts may arise. Bread is our most important single food. We may not always be so fortunate as to enjoy our present wide choice of other, more expensive foods, which presumably can compensate for any minor defects caused by flour improvement in the nutritive value of bread. If nothing else, therefore, it would seem a good insurance against any possible future curtailment in food supplies to continue studies on how flour can best be made into bread which retains the highest nutritional value. If any improver, such as chlorine dioxide, causes even slight defects in the nutritive value, as evidenced by any of the methods of investigation at our disposal, research should be intensified on the use of alternative improvers. The recommendation of the Food Standards Committee on the need for further investigation must therefore be fully endorsed. Admittedly the difficulties in detecting slight defects in nutritive value, except for losses in vitamin E and other substances which can be estimated chemically, are formidable. Tests for slight toxicity, which may easily be confused with loss of nutritive value, are perhaps even more difficult. H. B. Stoner[7] has at least made a start in attacking the problems to be faced in conducting long-term feeding trials.

From the consumer's point of view we may question whether the millers and bakers can be confident that the bread they produce has reached the highest attainable standards in taste and texture. Mass-produced British bread does not always compare favourably, except in whiteness and porosity, with bread in other countries, in many of which improvers are not allowed and baking methods are less sophisticated.[2] We should not be satisfied with bread which is less wholesome, less nutritious, or less palatable than the skill of man can make it. The use, or disuse, of flour improvers in helping towards the attainment of this ideal should be an urgent subject for further intensified research by toxicologists, nutritionists, and baking experts, aided by competent and unbiased tasting panels.

INSULIN ANTAGONISM AND HUMAN DIABETES

In the two decades which followed the discovery of insulin it became clear that other endocrine glands, notably the pituitary and the adrenals, secreted principles which could antagonize the effects of insulin in experimental animals. It seemed likely that

similar antagonists were effective in man, for patients with acromegaly were found to be relatively insensitive to injected insulin,[1] whereas patients with hypopituitarism were unusually sensitive to it.[2] With the knowledge, too, that extracts of anterior pituitary could bring about permanent diabetes in dogs,[3] it was natural to wonder if these endocrine factors might also be concerned in some way with the pathogenesis of human diabetes, and views of this kind were put forward by H. P. Himsworth.[4] A number of investigations have suggested that antagonists to insulin circulate in the blood of animals, and are dependent on both the pituitary and the adrenal glands for their activity. Recently many workers have attempted to study factors of this kind in the serum of diabetics, and much interest has been shown latterly in one substance of this nature described by Vallance-Owen and Lilley.[5 6] This substance, as yet unidentified, is intimately associated with serum albumin; it antagonizes the effects of insulin in causing an increased uptake of glucose by muscle tissue. This factor, which Vallance-Owen believes to be dependent on both pituitary and adrenals,[7] appears to be present in greater quantity in the serum of diabetic (and pre-diabetic) subjects than normal people. Vallance-Owen has speculated that the increased quantities of this material present in diabetes might be associated with the vascular complications that sometimes develop.

Not all workers are agreed that this factor is dependent on the pituitary, and recently C. Lowy, G. Blanchard, and D. Phear[8] have adduced some contrary evidence. Whether this factor, too, is the only one concerned in antagonizing insulin in serum also seems far from certain. Insulin antagonists have now been described in fractions of human serum protein by several groups of workers,[9-12] and pituitary dependence has been claimed for one of these substances by K. W. Taylor, L. Vargas, and P. J. Randle.[13] Several of these factors appear to be associated with ketosis, and differ in a number of properties from the albumin antagonist. Since very different experimental conditions have been used by various investigators to fractionate these substances in serum, it is possible that at least some of them represent the same substance, whose properties have been modified by the method of fractionation employed. The possibility that the ketone bodies themselves may also act as insulin antagonists has recently been raised by J. H. Ottoway,[14] who has shown that acetoacetate, for example, is able to depress the uptake of glucose by muscle. Adrenaline, too, seems able to function as an insulin antagonist in some circumstances.[15]

Much further work therefore remains to be done before it can be decided with certainty which of these substances is physiologically active, and it may be misleading to attempt to ascribe all the varied pathology of diabetes to any one of them exclusively. Nevertheless substances of this type seem likely to alter our ideas about the aetiology of diabetes. Thus recent work has suggested that considerable quantities of insulin may circulate in the early stages of untreated human diabetes, though its biological effectiveness is reduced or even abolished by the presence of antagonistic substances.[11 16] The presence of this insulin may not always be apparent in whole serum, though by protein fractionation it can be detected by separating it from the antagonists. Thus in some kinds of early diabetes the paradoxical situation might arise in which adequate amounts of insulin are present in the serum but the hormonally dependent antagonists prevent it from working.[17] Opinion is therefore moving away from the simpler view that diabetes is often associated with primary deficiency of insulin, at least in its early stages. Ultimately, though, when the islet cells become exhausted, the type of diabetes referred to by R. D. Lawrence as "absolute diabetes" may supervene.[18]

It may be asked whether or not these newer views on the aetiology of diabetes have any bearing on the treatment of the disease itself. If biologically active insulin is being secreted early in diabetes, then to what extent is insulin, or oral hypoglycaemic therapy, useful in preventing the deterioration of the islet cells? Are antagonists of this kind concerned in any way with the genesis of diabetic vascular complications? An association between one such substance and retinopathy has been claimed for one of the antagonists.[19] Satisfactory data for the other antagonists have not so far been published. If such an association between a pituitary dependent antagonist and the development of vascular complications could be unequivocally shown added weight would undoubtedly be given to hypophysectomy or section of the pituitary stalk as measures to prevent worsening of the vascular complications

[1] Davidoff, L. H., and Cushing, H., *Arch. Intern. Med.*, 1927, **39**, 751.
[2] Fraser, R., and Smith, P., *Quart. J. Med.* (New Series), 1941, **10**, 297.
[3] Young, F. G., *Lancet*, 1937, **2**, 372.
[4] Himsworth, H. P., ibid., 1949, **1**, 465.
[5] Vallance-Owen, J., and Lilley, M. D., ibid., 1961, **1**, 804.
[6] —— —— ibid., 1961, **1**, 806.
[7] —— —— Dennes, E., and Campbell, P. N., ibid., 1958, **2**, 696.
[8] Lowy, C., Blanchard, G., and Phear, D., ibid., 1961, **1**, 802.
[9] Baird, C. W., and Bornstein, J., ibid., 1957, **1**, 1111.
[10] Field, J. B., Tietze, F., and Steeten, D., *J. clin. Invest.*, 1957, **36**, 1588.
[11] Willebrands, A. F., and Sandwijk, J. C., *Clin. chim. Acta*, 1960, **5**, 508.
[12] Vargas, L., Taylor, K. W., and Randle, P. J., *Biochem. J.*, 1960, **77**, 43.
[13] Taylor, K. W., Vargas, L., and Randle, P. J., *Lancet*, 1960, **1**, 1313.
[14] Ottoway, J. H., *J. Endocr.*, 1961, **21**, 443.
[15] Groen, J., v.d. Geld, H., Bolinger, R. E., and Willebrands, A. F., *Diabetes*, 1958, **7**, 272.
[16] Steinke, J., Taylor, K. W., and Renold, A. E., *Lancet*, 1961, **1**, 30.
[17] Randle, P. J., in *Modern Trends in Endocrinology*, edited by H. Gardiner-Hill. London, 1958.
[18] Lawrence, R. D., *Brit. med. J.*, 1951, **1**, 373.
[19] Bornstein, J., and Hyde, D. M., *Diabetes*, 1959, **8**, 92.

of diabetes. The devising of a satisfactory procedure for assaying substances of this nature would go far to answer these problems.

The pendulum has therefore swung towards incriminating the pituitary in the pathogenesis of human diabetes. But it is still too early to be certain that it will not once again swing back towards the pancreas. Further work on insulin antagonists in diabetes will be awaited with great interest.

RECOVERY FROM DROWNING

During 1959 the Registrar-General recorded that 1,478 persons died from drowning in England and Wales. Probably at least as many were saved from drowning during the same period by prompt rescue, with or without resuscitation. This is partly illustrated in the awards of the Royal Humane Society for 1960, in which 152 of 220 persons promptly rescued from water in a semiconscious or unconscious state survived. Apparently in the survivors submersion had not been sufficiently long for the disastrous fluid and electrolyte changes described by H. G. Swann and N. R. Spafford[1] to occur.

It is thus to be expected that doctors fairly frequently have to treat patients whose recovery is delayed or incomplete, or who die later. Such cases are rarely reported, and K. W. Donald,[2] in his review of the literature, found only 12 cases of recovery, and details of 4 others are known. In these cases respiratory complications were frequent but usually mild, and there was recovery within a few days. Pulmonary oedema, pulmonary collapse, and mild bronchitis developed, and sometimes presented as "secondary shock" some hours later. The case (male) reported by C. E. Rath[3] was unique in that haemolysis, decerebrate rigidity, and temporary retention of nitrogen followed substantial absorption of fresh water into the circulation. Nevertheless the patient fully recovered.

Cases in which death was delayed are rarely reported, but again the records stress respiratory complications. In two out of three cases from the records of the Royal Humane Society for 1960 death was due to pneumonia. D. G. Rushton[4] in an examination of 64 fatal cases found only 2 in which death was delayed for a few hours, and in these a gross haemorrhagic inflammatory oedema of the lungs was found. In both these cases, as in most others of the series, there was ample evidence of inhalation of substantial amounts of water, based on the detection of algae in various organs. Such changes in the lungs may be responsible for the "secondary shock" and respiratory symptoms in survivors, and may well be a late reaction to contact between the alveolar surface and dirty and infected water. Giant sections and histological examination of the lungs in 54 cases showed no evidence of gross structural pulmonary damage, even when resuscitation had been vigorous and prolonged. The total number of recorded cases of permanent and even temporary recovery from drowning is thus small, but it may be concluded that the inhalation of substantial amounts of water is usually but not necessarily fatal.

Survival after immersion must, of course, depend on many factors, including a good state of health, a capacity to float and remain warm, the ability to hold breath, and the occurrence of glottic spasm, restricting the early entry of water into the lungs. Recovery would usually be expected under these conditions, either spontaneously or after brief resuscitation. Probably most survivors fall into this group. On the other hand, once considerable amounts of fresh or salt water have been inhaled, devastating changes in the blood volume and electrolytes will allow few people to survive more than a few minutes. It is thus apparent that in cases of drowning much more than asphyxia is involved. Nevertheless, in the few who survive this the best ways of treating the changes in the blood and body fluids, and the duration of treatment, are unknown. It is therefore important in these cases to look for evidence of haemolysis in blood and in urine, and for changes in blood electrolytes, haematocrit, and protein, while the patient should be kept under observation for an adequate period. Long-term effects of drowning on renal, cerebral, and pulmonary function have not been described, and thus evidence is lacking on what, if any, lasting damage there may be.

[1] Swann, H. G., and Spafford, N. R., *Tex. Rep. Biol. Med.*, 1951, **9**, 356.
[2] Donald, K. W., *Brit. med. J.*, 1955, **2**, 155.
[3] Rath, C. E., *Blood*, 1953, **8**, 1099.
[4] Rushton, D. G., 2nd International Meeting on Forensic Pathology and Medicine, 1960.

PIGMENTATION AND THE PITUITARY

Pigmentary changes in man and animals provide colourful testimony of the importance of hormones in the appearance of skin, hair, and feathers.[1] The skin darkens with pregnancy, for instance, and in Addison's disease, as well as in some cases of chronic hyperthyroidism and occasionally in diabetes, while in hypopituitarism it becomes pale. These may all be useful aids to diagnosis.

The shade of the complexion usually becomes darker after puberty; this deepening of pigmentation also involves the hair and eye colour. The genital and perineal regions are more affected than the surrounding skin. The melanin content of the skin from human castrates is lower than normal, whereas the carotene content is higher.[2] Administration of oestrogens to females in whom they are deficient results in hyperpigmentation of the nipples and genitalia.[3 4] The skin of eunuchoid males does not become pigmented after exposure to ultra-violet light unless the patients receive treatment with androgens.[5]

The pituitary in particular seems to hold pride of place in the function of controlling colour and shade. Thus ablation of the gland, whether by disease or by therapeutic measures, results in depigmentation of the

[1] Lerner, A. B., *Amer. J. Med.*, 1955, **19**, 919.
[2] Edwards, E. A., Hamilton, J. B., Duntley, S. Q., and Hubert, G., *Endocrinology*, 1941, **28**, 119.
[3] French, E. B., *Edinb. med. J.*, N.S., 1954, **61**, 225.
[4] Lerner, A. B., *Amer. J. Med.*, 1955, **19**, 917.
[5] Hamilton, J. B., and Hubert, G., *Science*, 1938, **88**, 481.
[6] McGuinness, B. W., M.D. Thesis, 1959, p. 196, Liverpool University.
[7] Calkins, E., Lerner, A. B., and Fitzpatrick, T. B., *Physiol. Rev.*, 1950, **30**, 91.
[8] Waldenström, J., *Acta endocr.* (*Kbh.*), 1950, **5**, 235.
[9] Fostvelt, G. A., *Proc. Soc. exp. Biol.* (*N.Y.*), 1939, **40**, 302.

skin. The change is now generally attributed to a lack of a pigment-producing hormone normally secreted by the pituitary and called melanocyte-stimulating hormone (M.S.H.). In lower animals that have three distinct pituitary lobes—e.g., the goat and cat—cells of the intermediate lobe are responsible for producing M.S.H. In man there is no distinct intermediate lobe, and the cells producing M.S.H. are situated in the posterior part of the anterior lobe of the pituitary.

Administration of M.S.H. to human subjects darkens the skin. This darkening is generalized, though deeper in exposed areas. If large doses are given to patients with hypopituitarism the pigmentation appears within two days,[6] while the skin returns to its previous pallor within a few weeks of giving the last dose. The effect of M.S.H. produced within the body is seen in Addison's disease, in which the pituitary attempts to stimulate damaged and inefficient adrenals by producing large amounts of A.C.T.H., at the same time producing excessive M.S.H.[7 8] Variations in skin colour in a person under stress, during the menstrual cycle, and in conditions of endocrine imbalance have also been attributed to fluctuations in melanin pigmentation under the influence of M.S.H. These changes, which are best observed in dark skin,[1] were the subject of a report by Dr. B. W. McGuinness at p. 563 of the *Journal* last week. He studied changes of skin pigmentation during the menstrual cycle in 63 young women, and considers that they may be due to variation in production of M.S.H. by the pituitary.

The melanocyte-stimulating hormone causes the skin to darken by accelerating growth of pigment cells and melanogenesis.[9] The sex hormones probably sensitize the skin to the action of M.S.H. and determine, to some extent, the distribution of pigmentation. Ultra-violet light serves as a photochemical catalyst,[5] accelerating production of melanin in the skin under the influence of sex hormones and M.S.H. Ultra-violet light is not, however, essential for the development of hyperpigmentation from melanin, since this can occur in places inaccessible to it, such as the vagina and pharynx.

EXAMINATION OF NURSES

The General Nursing Council for England and Wales is to introduce changes in the final examination for registration on the general part of the Register of Nurses. Miss M. M. C. Louden, F.R.C.S., draws attention to this in a letter at page 648 and appeals for additional examiners from the medical profession. Miss Louden refers to the criticisms made of the set questions nurses have been subjected to in examinations, and adds that the majority of nurses are quite able to answer them. Here are some of the questions set in June this year:

"1. Enumerate the causes of heart disease. What are the symptoms and signs of congestive cardiac failure? Describe the treatment of this condition.

"2. Describe the symptoms, signs, and complications of diabetes mellitus. Discuss the management and treatment of this condition.

"3. Give an account of the drugs which may be used in the treatment of the following conditions, indicating dosage and dangers: (*a*) duodenal ulcer; (*b*) acute pyelitis; (*c*) rheumatoid arthritis."

It is easy to imagine the reactions to these of a girl thinking of going in for nursing and having a look at the examination papers in order to see what would be expected of her.

Doctors have shown plenty of healthy unrest during the past few years about the qualifying examinations in medicine. In the U.S.A. the final written examination plays a relatively small part in the final decision as to whether an undergraduate should be qualified to practise. But when it comes to nurses and nursing one may beg leave to doubt the educational value of papers which would be well suited for a qualifying examination in medicine. Is this kind of ordeal by examination really necessary to good nursing? Or is it being imposed by doctors from on high?

SAFETY ON THE ROADS

Much of the report[1] of the Road Research Board is concerned with technical problems of road construction. Nevertheless the type of research undertaken has been largely influenced by the continuing and alarming rise in road accidents. The casualties in 1960 (7,000 killed and more than 340,000 injured) were the highest so far recorded. The report suggests that motorways may help to reduce accidents, for when all the accidents occurring during its first year of operation on the London–Birmingham motorway are added to those which occurred during the same period on the main roads by-passed by the motorway and the total is compared with the number of accidents which occurred on the main roads before the motorway opened, then it is tentatively estimated that in one year the motorway resulted in an overall saving of 600 to 800 casualties, including 20 to 30 fatalities. More precise estimates are to be published later.

The frequency and seriousness of head injuries are once again emphasized; the report mentions that in some of the cases investigated the severity of the injuries sustained might have been substantially reduced if seat-belts or harness had been worn. But it will remain difficult to obtain a reliable assessment of the value of seat belts until more are in use. Some thought is being given to the provision of windscreens that might yield or be ejected under the loading imposed by the head of a person coming into violent contact with it.

An investigation carried out in the Metropolitan Police District showed that the fatal and serious casualty rate in the dark was about twice that in daylight, this ratio showing no variation from one month to another. About 50% of the accidents occurring to drivers under 25 happened in the dark: the older the driver the smaller the proportion became. The chance of being involved in a serious accident per mile travelled during daylight hours was twice as great for the young under 19 and the old (over 70) as for those of middle age (40–45).

[1] Department of Scientific and Industrial Research, *Road Research, 1960*, H.M.S.O., London, 1961. Price 7s. net.

In several countries where speed limits have been imposed observers have found that, although the proportion of vehicles travelling at a high speed has been reduced, nevertheless "a high proportion" of vehicles exceed the limit. The imposition of speed limits in built-up areas in Switzerland, the Netherlands, Great Britain, Germany, and Sweden coincided with a reduction in the number of fatalities; and speed limits imposed at week-ends on motorways in Germany and along main roads near London and national roads in France were associated with falls in the numbers of serious accidents. As for overtaking, controlled studies showed that even skilled drivers take more risks in overtaking at high speeds than at low ones: the safety margins they allowed themselves were sometimes dangerously small. This is a finding which all who consider themselves fast yet safe drivers should take to heart.

G.P.s IN HOSPITALS

The Hospital Subcommittee of the General Medical Services Committee has finished its examination of the proposals made in the Platt Report for employing general practitioners in hospitals. With minor modifications the Subcommittee's report has been adopted by the G.M.S.C. and will be forwarded to the Ministry of Health. It appears at page 131 of this week's *Supplement*.

General practitioners have for some time been knocking hard at the doors of N.H.S. hospitals, and a multiplicity of Ministers of Health have admitted the desirability of their getting back into the hospitals from which they were ousted when the N.H.S. was introduced. As might be expected, therefore, the G.M.S.C. welcomes "opportunities to co-operate again in the hospital field." It hopes, too, that general practitioners with the ability and experience will be able to play their full part in hospital work, and that some will have the opportunity to reach consultant status.

The Committee approaches the new assistant grade with some caution and is anxious that it should not become another S.H.M.O. appointment under a different name. It favours an early review of hospital medical staffing, and wishes to see general practitioners represented in such a review at every level. And when general practitioners do enter hospital life and work the Committee wants to ensure that they shall have the full clinical responsibility that is theirs in their own practice, and that they should have proper status and security of tenure. Stress is laid on incentives, and the G.M.S.C. comes down firmly against paying out of the central pool for work done by general practitioners in hospital. With the shortage of medical man-power to-day it is concerned with the dangers of calling in the help of general practitioners in an attempt to solve the present hospital situation. For a number of years there will have to be a careful balance in the distribution of doctors in hospitals and in general practice.

In these days of intense specialization the general practitioner should come to occupy the position formerly held by the general consultant. If this is a correct interpretation of the situation then the general practitioner should hold an important position in the hospital, for it is principally by close contact with hospital work that he will be able to keep abreast with the growing complexities of modern medicine. The implications of such a thesis need to be carefully thought out if the desired and desirable return of general practitioners into hospital work is to take place with general benefit to medicine and so to patients in need of medical care. An undesirable course would be to utilize general practitioners merely to extract the hospital service from some of its present dilemmas.

MODE OF ACTION OF THE PENICILLINS

Since the first discovery of penicillin, many theories have been put forward to account for its action on bacteria. Large distorted forms of the organisms were seen in penicillin-treated cultures, and as early as 1946[1] it was suggested that action of the antibiotic on surface structures of the organisms might be responsible for the deformation. In 1957 J. T. Park and J. L. Strominger[2] again suggested from biochemical observations that penicillin acts on the sites of formation of the cell walls of bacteria. Strong evidence[3,4] is now available that not only benzylpenicillin but also the new penicillins, such as methicillin, have as their primary action the inhibition of formation of the mucopeptides in cell walls of micro-organisms, and have no other direct effects on the functions of the cell. Since the mucopeptides are the principal structural components of the cell walls, many aspects of penicillin action can now be more readily understood. For example, the reason why penicillin acts only on multiplying bacteria is presumably because restriction of the increase in size of the organisms' overcoat becomes dangerous only when internal growth still occurs and can lead to its rupture. The specificity of the penicillins in distinguishing between the parasite and the host is explicable in terms of the unique chemical nature of the mucopeptides. These all contain the sugar derivative muramic acid, which has not so far been found in mammalian tissues, and a few amino-acids, some in the D configuration. Moreover, the very small amount of mucopeptide[5] present in the walls of Gram-negative organisms may partly explain their relative resistance to the penicillins.

Resistance to the penicillins can be of two types. Bacteria may produce an enzyme—penicillinase—which destroys benzylpenicillin. Alternatively, the mechanism by which the bacteria form the cell wall may become insusceptible to the antibiotic. In the patient it is production of penicillinase which makes the staphylococcus resistant to benzylpenicillin, but this enzyme has very little action on methicillin. Staphylococci resistant to the latter drug may perhaps use the second type of mechanism, as do mutant staphylococci selected in the laboratory. Organisms producing a specific methicillinase have not, so far, been encountered.

[1] Duguid, J. P., *Edinb. med. J.*, 1946, **53**, 401.
[2] Park, J. T., and Strominger, J. L., *Science*, 1957, **125**, 99.
[3] Mandelstam, J., and Rogers, H. J., *Biochem. J.*, 1959, **72**, 654.
[4] Rogers, H. J., and Jeljaszewicz, J., ibid., 1961, **80**, 6P.
[5] Mandelstam, J., *Nature (Lond.)*, 1961, **189**, 855.

Clinicopathological Conference

OXALOSIS IN AN ADULT

DEMONSTRATED AT THE

POSTGRADUATE MEDICAL SCHOOL OF LONDON

This is the case of a man with renal calculi who developed uraemia. Despite repeated haemodialyses with an artificial kidney at Hammersmith Hospital, he died with cardiac and pulmonary complications (Case No. 245,371; P.M. No. 9,457).

Clinical History

Dr. M. D. MILNE: The patient we are discussing to-day was a male, aged 58 at the time of his death in November, 1960. He was in good health until March, 1954, when he had right-sided ureteric colic. An intravenous pyelogram showed a calculus in the right ureter causing a right hydronephrosis. In November, 1954, a retrograde pyelogram showed that he had passed the stone, but the hydronephrosis was still present. Three years later, after an attack of left renal colic, an intravenous pyelogram showed that there was a calculus in the left ureter.

In April, 1958, another pyelogram showed good secretion on both sides, but there was an opacity in the upper pole of the left kidney. He had passed a calculus, and analysis proved it to be a mixed stone consisting of calcium phosphate and calcium oxalate.

HAEMODIALYSIS

Early in September, 1960, he was admitted to another hospital with frequency of micturition and pain in the left loin. The blood urea on admission was 120 mg./100 ml., but this had risen to a value of 520 mg. one month later. There was progressive deterioration of his general condition, with repeated uraemic vomiting. The blood-pressure was slightly raised to 190/100, and *x*-ray of his abdomen showed calcification over both kidneys and a left ureteric calculus. The serum calcium was normal. He became progressively more oliguric and the plasma potassium rose to 7.2 mEq/litre. He was therefore transferred to Hammersmith Hospital for treatment by haemodialysis.

On admission he was lucid and co-operative, the pulse was regular, and the blood-pressure 155/85. Rectal examination showed a moderately enlarged prostate. The urine contained a trace of protein, and there were casts and some red blood cells in the deposit. He was anaemic, the haemoglobin being 8.2 g./100 ml. and the blood urea was 570 mg. There was severe uraemic acidosis with reduction of the plasma bicarbonate to 10 mEq/litre. He was treated by repeated haemodialysis on a rotating-coil artificial kidney together with one period of peritoneal dialysis.

TERMINAL ILLNESS

Early in October *x*-ray examination showed a normal heart with clear lung fields, but three weeks later the heart was grossly enlarged and there was pericardial friction. Electrocardiogram showed ST changes suggestive of pericarditis. He was thought to have uraemic pericarditis with effusion, but as there was no evidence of pericardial tamponade no paracentesis was attempted. At this time he developed acute arthritis of the feet and fingers which was diagnosed as secondary gout. There was haemoptysis, and *x*-ray showed an opacity at the right lung base, interpreted as a pulmonary infarct. One month after admission he complained of failing vision, and ophthalmoscopy showed multiple haemorrhages and exudates but no papilloedema. By mid-November he was very ill and breathless. There were crepitations at both lung bases, and *x*-ray showed opacities suggestive of bilateral pulmonary oedema. There was now rapid physical and mental deterioration, and blood culture was positive, there being a growth of *Staphylococcus pyogenes* resistant to penicillin, streptomycin, and tetracycline, but sensitive to chloramphenicol. He was still severely uraemic, the blood urea being 380 mg. per 100 ml. He died in uraemic coma the same day.

Clinical Diagnosis

(1) Bilateral renal calculi and nephrocalcinosis.
(2) Mixed calcium phosphate and oxalate calculi.
(3) Uraemia due to chronic calculous pyelonephritis.
(4) Uraemic pericarditis with effusion.
(5) Infarcts and oedema of lung bases.
(6) Terminal staphylococcal septicaemia.

Post-mortem Findings

Dr. B. E. HEARD: A tall, well-built man, 6 ft. 7 in. (1.98 m.) in height, with oedema of legs. There were "teflon" tubes inserted into the left forearm.

There was an effusion of 1 litre of slightly turbid straw-coloured fluid in the *right pleural sac*, but the *left sac* was obliterated by dense fibrous adhesions. There was 1 litre of similar fluid in the *peritoneum*. The pericardium contained a moderately blood-stained, fibrinous exudate and was lined by fibrin. The *heart* weighed 580 g. (normal=about 400 g.), and the *left ventricle* was hypertrophied to 1.8 cm. The *right ventricle* was normal. There was no evidence of ischaemia. All valves were normal and the *coronary arteries* showed only mild atherosclerosis. The *aorta* showed occasional, old, calcified plaques in the arch, and these increased in the descending portion. There was a heavy deposit of calcium oxalate crystals in the centre of the media (Fig. 8), except beneath intimal plaques, when the crystals were then in the plaques themselves.

The *trachea* and main *bronchi* were congested and contained a little mucopus. Both *lungs* (left=950 g., right=920 g.; normal left=400 g., right=450 g.) showed oedema and bronchopneumonia. No uraemic oedema was present. The *tongue, oesophagus, stomach*, and *intestines* were normal. The *liver* (2,165 g., normal =1,600 g.) showed no histological changes. The *gall-bladder* and *bile ducts* were normal. The *pancreas* was normal.

The *right kidney* weighed 180 g. and the *left kidney* 135 g. (normal=170 g. each). They were surrounded by rather fibrous adipose tissue which was dissected with difficulty from the renal capsules. The capsules themselves were adherent to the cortices, and the stripped

surfaces showed a coarse granularity. The cut surface showed shrinkage of the parenchyma. The *right pelvis* was dilated (Fig. 4). Throughout both kidneys there were enormous numbers of small crystals of calcium oxalate (Fig. 5). Under the dissecting microscope they resembled grains of sand, and were most plentiful in the cortex. Near the tips of papillae, oxalate calculi up to 3 mm. across were observed (Fig. 4), sitting in small pits in the calices. Histologically the majority of the crystals lay in the convoluted tubules and were doubly refractile (Figs. 2 and 3). They were in roughly spherical collections and had irregular outlines for the most part, but occasionally they were seen to radiate regularly from the centre. Large numbers of cortical tubules had disappeared, glomeruli were closer together,

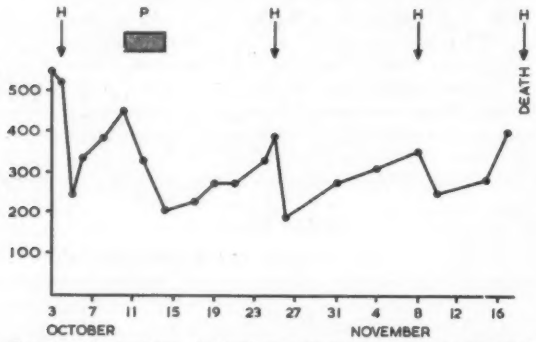


FIG. 1.—Fluctuations of blood urea during the patient's terminal illness. H indicates haemodialysis with a Kolff rotating-coil artificial kidney, lasting for six hours. P indicates a period of peritoneal dialysis lasting three days. Note that the artificial kidney achieves as much in six hours as peritoneal dialysis in three days. The patient died shortly after the fourth haemodialysis.

and the cortex was infiltrated by a large number of lymphocytes. Many glomeruli were undergoing fibrous atrophy, and an occasional one showed a central calcium oxalate crystal. There was only a little intimal thickening of the arteries, and their walls were free of crystals. A naphthachrome green B stain confirmed the presence of calcium. A section of the trachea showed no crystals. The *right ureter* was slightly dilated but free of calculi. A few minute calculi had collected at the lower end of the *left ureter*, and there were a few in the *bladder*. *Prostate* and *testes* were normal.

The *spleen* weighed 360 g. (normal=170 g.) and was congested, and showed no crystals or other abnormal features histologically. The *adrenals* were normal. The *thyroid* was enlarged, weighing 75 g. (normal=30 g.), and histologically it was a nodular colloid goitre. The parathyroids appeared normal grossly, and histologically showed some fat cells. The *brain* weighed 1,522 g. (normal=1,400 g.). One-centimetre frontal slices revealed no abnormality. Several blocks from cortex, basal ganglia, and cerebellum showed no oxalate crystals.

In the proximal interphalangeal joint of the *right forefinger* were a number of white flecks in the synovial membrane. Histologically there were some oxalate crystals here and there. Schultz stain for urates, in alcohol-fixed preparations, was negative on kidney and synovium. The *vertebral marrow* was normal grossly and microscopically. The trabeculae were strong, and an undecalcified section showed normal osteoid seams.

Examination of a few stones from the renal pelvis by Dr. I. Wootton: "Stones contained a large amount of oxalate and a small amount of phosphate."

Sections of various tissues were screened by polarized light for oxalate crystals. They were found in the tongue (mostly in the media of small arteries), abdominal lymph nodes, stomach (muscle coat), apical scar of lung (Fig. 6), heart (Fig. 7) (numerous here), sublingual gland (in patches of chronic inflammation), seminal vesicles (within the lumen), as well as kidney (Fig. 3) and aorta (Fig. 8) as mentioned above.

Pathologist's Diagnosis

(1) Uraemia.
(2) Renal calculi (oxalates),
(3) Oxalosis of numerous organs.
(4) Bronchopneumonia.

Discussion

Dr. MILNE: We had not suspected this widespread unusual disease in life and I think we now have to discuss the diagnosis and give definitions. I am going to restrict myself to the oxalate findings and leave others to discuss this aspect and fill in the other issues.

First of all, let us have definitions. Oxalosis is defined as a condition in which there are oxalate deposits elsewhere than in the kidney; if you include the kidney you can get mixed up with all sorts of nephrocalcinosis, renal stones, and so on, so I think you *must* say elsewhere than in the kidney, and on this definition this man undoubtedly had oxalosis. Now what do we mean by hyperoxaluria? Well, I suppose this is very simple: it simply means that the patient is putting out in the urine more oxalate than the upper limit of normal. The upper limit of normal in the adult is 40 mg./day. Unfortunately we never measured the urinary oxalate in life, as we should have done. Possibly, however, the results during the time he was under our care might have been unreliable, because when a patient becomes uraemic the amount of a substance put out in the urine gets less well defined. This is well seen in various diseases we know more about, for instance, in the much more common disease of cystinosis where there is aminoaciduria. When children with cystinosis become uraemic the amino-acid excretion falls. In other words, the diagnosis is much easier in the earlier non-uraemic stage of these diseases.

HEREDITARY HYPEROXALURIA

This is not my complete list of definitions. What do we mean by hereditary hyperoxaluria with oxalosis? This is undoubtedly a recessive hereditary disorder of metabolism which has been recently well investigated, particularly in London at St. Bartholomew's Hospital and also in America. Fig. 9 shows the age grouping in this disease. It is primarily a disease of childhood

FIG. 2.—Kidney showing numerous crystals of calcium oxalate scattered through cortex. They have been slightly moved by the microtome knife. Three glomeruli show thickening of Bowman's capsule. There is interstitial fibrosis and tubular atrophy. Several foci of lymphocytes. (H. and E. ×56).

FIG. 3.—Same section of kidney as in Fig. 2 photographed with polarized light, showing anisotropic crystals of calcium oxalate. (H. and E. ×56.)

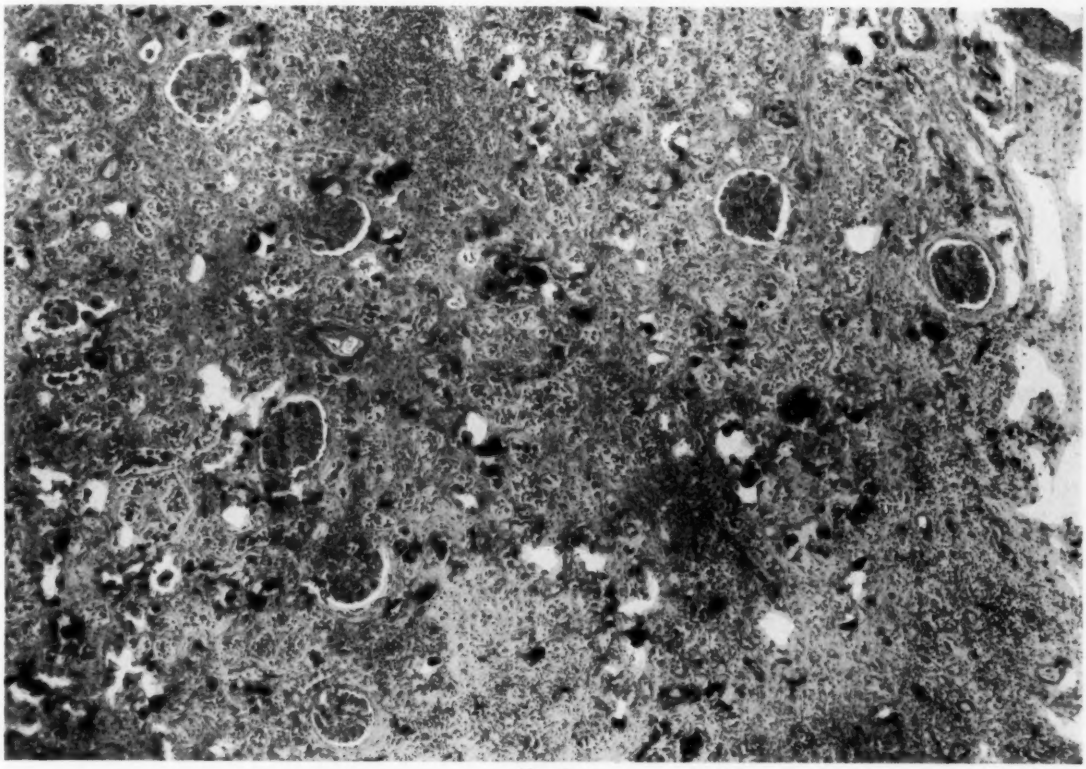


FIG. 2

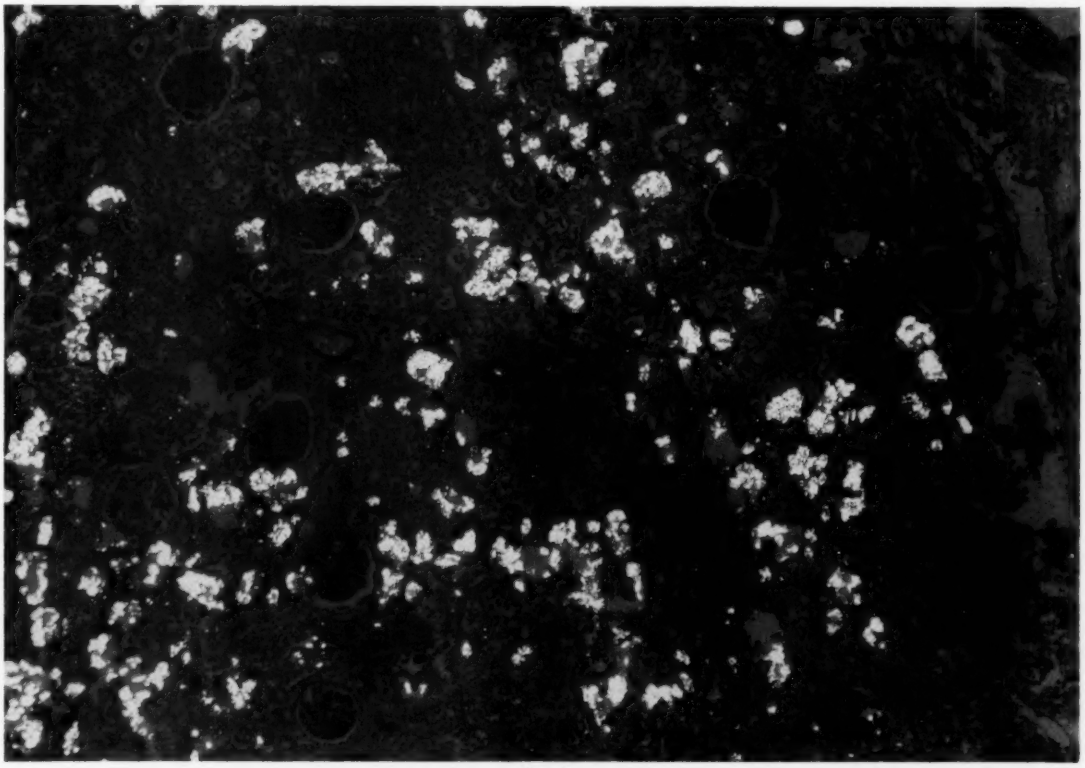


FIG. 3

FIG. 4

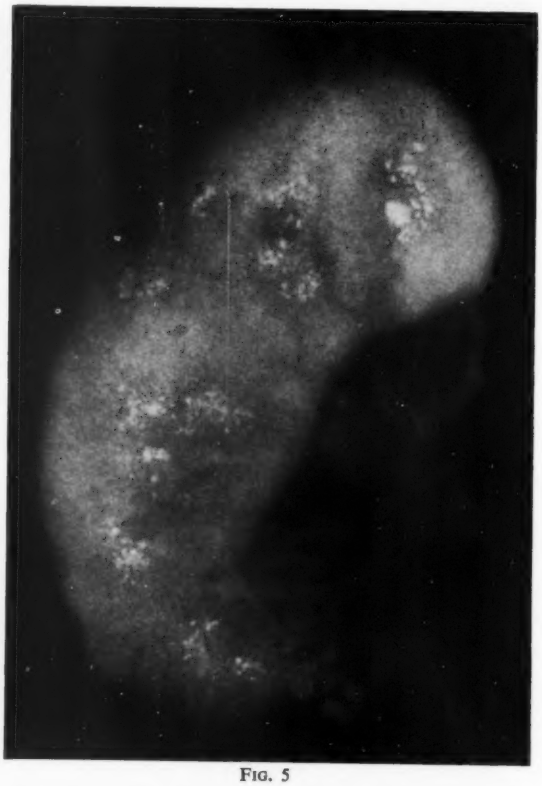


FIG. 5

FIG. 6

FIG. 7

FIG. 8

and early adolescence. In Fig. 9 are charted 19 undoubted cases, showing the age when the first symptom of the disease occurred, and when death occurred. The disease has a high mortality, the patients usually dying of renal failure in childhood or adolescence. The great majority of cases start about the age of 4, and the mean age of death is about 14. The last case is perhaps atypical: the disease started at age 12 and the patient is still living at the age of 31. These are proved cases of congenital hyperoxaluria with oxalosis.

How do we diagnose this disease with certainty? We like to have a recessive family history, we like to know if they are putting out more oxalate than is normal in the urine, we like to see evidence of oxalosis at necropsy. The only evidence we have got in the present case is the oxalosis at necropsy. We also know that a brother of this man died of renal calculus disease. But at present we have not got the records from the other hospital to see whether there is any similarity to our case. So we cannot be absolutely certain about the family history. All we know is the oxalosis. Now what about oxalosis in adults? Well, this has occurred, but it has never been proved to be an identical condition to the well-known hereditary disorder of metabolism I have described. The answer is that all of the adult patients so far in the literature have been like this man, uraemic, and in no case has an oxalate determination been made in life. There is only, so far as I know, one other instance in the literature[1] where more than one member of a family has been affected. In this report the two cases are very like our patient, but there is no absolute proof that the disease is identical with the disease of childhood. There are warnings that we should be guided by age very often in these hereditary diseases. For instance, we are quite certain now that the childhood and adult forms of Fanconi disease are quite different diseases, and similarly the infantile and adult types of renal tubular acidosis.

METABOLIC DISORDER

Finally, what do we know of the actual metabolic disorder of primary hyperoxaluria? Fig. 10 shows a rather complex metabolic chart, but it does indicate that we think the oxalic acid in this disease is derived from glycine. This, of course, is a common amino-acid of proteins. Gelatin in fact contains 40% glycine, and we could never make a glycine-free diet in treatment. In any case, many other amino-acids are converted to glycine, so we have no means of treating this disease to date. All we know is that the high concentration of glyoxylic acid which is responsible for the formation of excess oxalate probably comes from glycine. Now glyoxylic acid, the key substance in this metabolic path-

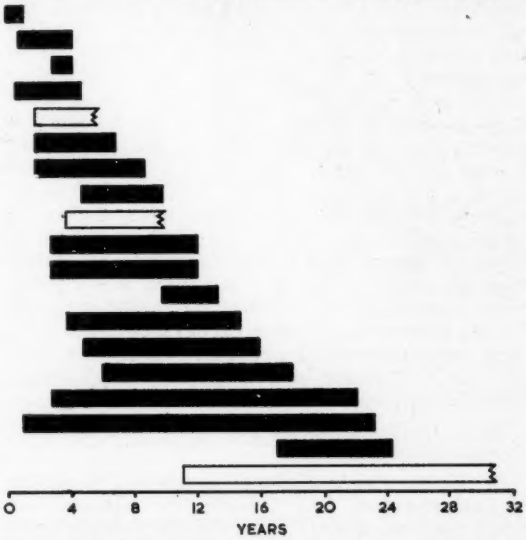


FIG. 9.—Age at first symptom and at death in 19 proved cases of primary hyperoxaluria. Unshaded columns indicate patients still alive when recorded in the literature. The disease usually starts in early childhood and causes death in adolescence or early adult life.

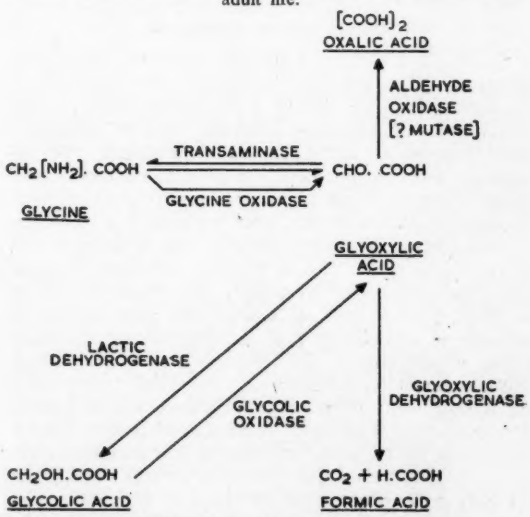


FIG. 10.—Summary scheme of metabolism of glycine, and glyoxylic and oxalic acids. Oxalic acid is formed in excess if glyoxylic acid is present in high concentration in body fluids. In primary hyperoxaluria an enzyme which normally metabolizes glyoxylic acid must be deficient. In the rat glycine-α-ketoglutonate transaminase is the major enzyme which removes glyoxylic acid. If human metabolism is similar to the rat, this is likely to be the deficient enzyme in the disease.

way, can be made from glycine in two ways, either by transamination, or by oxidation by glycine oxidase. We do know that when there is a high concentration of glyoxylic acid in the body fluids there is very rapid conversion to oxalate which is deposited in various tissues. So that in the disease of primary hyperoxaluria there must be some defect in the metabolism of

[1] Edwards, D. L., *Arch. Path. (Chicago)*, 1957, **64**, 546.

FIG. 4.—Right kidney showing dilatation of pelvis, narrowing of parenchyma, and oxalate stones (arrowed) in and around papillae and upper pole of kidney.

FIG. 5.—Post-mortem radiograph of right kidney showing radiopacity of fine deposits of calcium oxalate in cortex and of coarse deposits in medulla.

FIG. 6.—Apical scar of lung, photographed with polarized light, with fibrous pleural thickening in left upper quadrant of photograph, and scarred lung elsewhere. There are some anisotropic crystals of calcium oxalate among the closely packed elastic fibres. (Elastic–van Gieson. ×100.)

FIG. 7.—Myocardium photographed with polarized light, showing anisotropic crystals of calcium oxalate. (H. and E. ×38.)

FIG. 8.—Aorta, photographed with polarized light, showing narrow band of anisotropic crystals of calcium oxalate in centre of media. (H. and E. ×50.)

glyoxylic acid whereby it accumulates in high concentration in body fluids and is converted to oxalate, which is deposited in the kidneys and various other tissues.

We only have accurate data from that useful laboratory animal the rat, and I cannot guarantee that the rat is identical with man in this respect. There are four ways in which glyoxylic acid is known to be metabolized: by (*a*) degradation, (*b*) reduction to glycolic acid, (*c*) oxidation to oxalic acid, and (*d*) back-transamination to glycine. Now in the rat this last pathway is by far the most important method, so that, if—and this is a big if—man is like the rat, the basic defect in primary hyperoxaluria is lack of the enzyme glycine-α-ketoglutonate transaminase, which is the main agent in safely reducing the level of glyoxylic acid in blood. If this enzyme is absent and the blood glyoxalate rises, the excess glyoxalate is converted to the highly injurious substance oxalate, which is deposited in tissues. Further study of the basic disorder of the disease is going on in many parts of the world, but whether the adult cases are even similar in metabolism to the childhood cases, I do not know.

Dr. C. C. BOOTH: Could you tell us what pyridoxal phosphate does?

Dr. MILNE: Pyridoxal phosphate acts as a co-enzyme to transamination, and therefore the transaminases would not work if there was a deficiency of pyridoxal phosphate. These cases have been tested by classic means for pyridoxine-deficiency and have not shown any such deficiency.

ACUTE GOUTY ARTHRITIS

Dr. A. ST. J. DIXON: I saw this man when he had his attack of acute arthritis, and it certainly appeared to be gout. Like Dr. Milne, I would like to start with definitions. Tophaceous gout can only be diagnosed when one can see urate crystals in the tissues. We do not have this evidence here, but if we had it there could be no doubt about the diagnosis of gout. In about 60% of cases of gout, however, what we have is a medically observed acute arthritis associated with a raised serum level of uric acid. This is the state of affairs we have here, and this is what we usually get. Now this is not a 100% proven gout, and obviously other forms of arthritis in association with a raised serum uric acid could masquerade as it. However, it was an acute arthritis involving one foot and one hand which came on acutely, went down again fairly acutely, and I think we must accept it as gout. A clinical possibility, remote because of the collateral evidence, is that the association of pericarditis with acute arthritis in several joints might possibly have been rheumatic fever. I mention this only to exclude it. Thirdly, in view of the post-mortem evidence, there is another possibility which we might bear in mind—namely, that there may be an acute gout-like arthritis associated with oxalates even as ordinary gout is with urates; that, of course, is entirely speculation.

SECONDARY RENAL GOUT

For a long while there has been a controversy as to whether the frequent association of renal disease and gout can occur in two ways; on the one hand, renal disease may interfere with the excretion of uric acid, and the raised serum level of urates can lead in some way unknown to the development of an acute gouty arthritis. On the other hand, we know that patients who start with gout often develop complications in the kidneys. Clinically we find that about 30% of our cases at this hospital have fairly obvious evidence of renal disease. At necropsy almost 100% have some evidence of renal disease. Although in many cases the renal disease is not specific, it has been argued that nevertheless it is a consequence of hyperuric damage to the kidneys. It is a problem of which came first, the chicken or the egg. I think it is cases such as this which provide very strong evidence for secondary renal gout. Here is a man with a very peculiar metabolic condition which damaged his kidneys, and which, on the face of it at any rate, also occurred in his family. This must be accepted as the primary condition, and the gout as secondary. A possible contributory factor is that of repeated dialyses. Urea is a smaller crystalloid molecule than urate, and urate may be in part loosely bound to protein in circulation. Haemodialysis will selectively clear much more urea than urate from the blood.

NEPHROCALCINOSIS

Dr. R. E. STEINER: Now that we have definitions, Dr. Milne has brought up the question of nephrocalcinosis. As it happens, there is an excellent review in the current issue of the *British Journal of Urology*, from Pyrah and Hodkinson,[2] in which they give a very good definition of nephrocalcinosis. It is essentially a radiological diagnosis, and therefore it is a little difficult to be too certain about the distribution of the calcinosis, but the deposits of crystals which you saw to-day, and the stones, if one can talk about stones, were in close proximity to the papillae. It is surprising how on intravenous pyelography one can see in these patients quite normal papillae with a conglomeration of dense opacities just in the distal tubules. Once one of these smaller accretions breaks off into the collecting system it will form the nucleus of a stone. One must be careful to distinguish a stone which is within the calyx or pelvis, and which on the excretion pyelogram would show up within the pelvis, from classical nephrocalcinosis, which is not intracaliceal but just distal to the papillae in the terminal tubules. The other type of calcification demonstrated histologically—the crystals—was in the parenchyma. The crystals can be demonstrated by *x*-ray crystallography, but we cannot demonstrate them by radiographic methods.

Now Dr. Dixon mentioned that the diagnosis of calculous pyelonephritis was right. Well, this patient had got stones. Some of these crystals must have dropped into the pelvis and formed the basis of stones. We also saw stones down the ureter, and he had a hydronephrosis. So that when we get the combination of nephrocalcinosis, as we see it here—and undoubtedly he had got nephrocalcinosis—and renal stones, the distinction is difficult, and one has to rely largely on a good retrograde pyelogram to outline the renal papillae and demonstrate the calcifications. Pyrah mentions a very high instance of microscopic calcification in renal calculous disease. He put it as high as 60%. If one looks carefully, with the aid of *x*-ray crystallography one can pick up crystals in the parenchyma irrespective of their composition. Lastly, Pyrah and Hodkinson also quote two cases of oxaluric nephrocalcinosis, one of them probably of the type which we saw here to-day. This is a very comprehensive review, which deals with all types of nephrocalcinosis.

[2] Pyrah, L. N., and Hodkinson, A., *Brit. J. Urol.*, 1960, 32, 361.

Dr. BOOTH: Is it in fact true that in renal tubular acidosis, for instance, you fail to demonstrate the calcification on radiology in something like 50% of cases?

Dr. STEINER: It depends on the type of *x*-ray method. If you use crystallography this would show it; if you use ordinary *x*-ray, as we do it, you could not expect more than 50% positives.

ABSENCE OF TISSUE REACTION

Dr. HEARD: A notable feature of the histology was the absence of a reaction to the deposits, with no giant cells and no fibrosis. The crystals did tend to accumulate occasionally where there was fibrosis, for instance in the aortic atheroma, in the scar in the lung, and also one of the deposits in the left lung was especially associated with fibrosis. There was little fibrosis in the heart, however, and the muscle was normal but for the deposits. Experimentally glycine has been traced through to glyoxylate and oxalic acid in the heart muscle, so that there may be some local chemical reason for precipitation there, although it is rather a far cry from experimental work to the present case. The last thing is that the parathyroids were normal and the osteoid seams of the bones were quite normal also. This has been the experience of others in this condition.

Dr. C. PALLIS: Was there any cerebral oxalosis?

Dr. HEARD: Not in several blocks. I think we would have to take a large number of blocks to exclude it altogether. It certainly has been reported in the brain.

Dr. BOOTH: Isn't it extremely odd that this should have come on at the age of 58? I think you pointed out that this is a very unusual situation. I wondered if there was anything in the history here which might suggest he was a strawberry-eater or champagne-drinker or anything else that might have added to a pre-existing mild oxalosis.

DIAGNOSIS IN LIFE

Dr. MILNE: I would just like to tie some of these points together. I think we should not be too rigid in defining nephrocalcinosis as a purely radiological entity, although this is the only way I think that the diagnosis can be made in life. We cannot hope to do much with renal biopsy, because most of the nephrocalcinosis is in the medulla. If medullary tissue adjoining the renal pelvis is obtained, then the needle has gone too deep and you will get haematuria. We do not like getting deep medulla. Furthermore we think that percutaneous renal biopsy is more dangerous in nephrocalcinotic kidneys than in kidneys without calcification. Of course there is the much more delicate method of post-mortem demonstration of high calcium in the tissues, and I think perhaps we should define this as post-mortem nephrocalcinosis. This means it is demonstrable only at necropsy, and not radiologically.

I think the rare disorder in this patient is a different disease from the childhood cases because of the late age of onset. You have analogies, as I have said, in Fanconi's syndrome and renal tubular acidosis. With regard to tissue reaction to these crystals, this has been worked on most clearly in the condition of cystinosis where cystine crystals get deposited in tissue. Now here there is absolutely no fibrous reaction at all to naturally formed cystine crystals. But if one injects a suspension of cystine experimentally, subcutaneously or intramuscularly, in the experimental animal, one gets a most intense inflammatory and fibrous reaction. The usual explanation for this is that in cystinosis the crystals form within the cells to start with, and that one only gets the inflammatory reaction if crystals are injected into the extracellular space. I would have thought that the lack of reaction to these oxalate crystals, and our knowledge of the metabolism of oxalates, suggest that the crystals were formed within the cells in the first place. In other words, the first deposition of oxalate crystals was in the intracellular fluid and not in the extracellular fluid. As far as I know dietary oxalate has little to do with them. There has never been any demonstration that oxalosis is due to a high dietary oxalate, and I myself would have thought that one could only get oxalosis by some, at present unknown, disorder of metabolism.

We are grateful to Dr. J. P. Shillingford and Dr. B. E. Heard for assistance in preparing this report, to Mrs. Helen Jeacock for secretarial work, and to Mr. W. Brackenbury for the photographs.

Nova et Vetera

SEMMELWEIS

This book* should be read by all who find it difficult to accept new methods of treatment. It is an object lesson (or should it be subject lesson?). The author states that "as a martyr to the world's stupidity Semmelweis is one of the great tragic figures of all history." Of medical history, certainly. He discovered a method of preventing one of the greatest scourges of his time—childbed or puerperal fever—but his senior colleagues refused to investigate his claim, actively opposed his methods, and hindered his advancement. That men should be so indifferent when the death-rate from puerperal fever after normal labour in healthy women in some clinics was over 10% seems incredible, but unfortunately it was true. This account is so well written that the reader becomes exasperated as he learns of such ignorance and malignant stupidity.

Semmelweis, when once he had demonstrated the efficacy of his methods to his own satisfaction and that of a few friends, trusted too much to the view that "truth must prevail," forgetting that the element of time is not included in the aphorism. He wrote little, and what he did write was too diffuse and discursive. If he had lived two more decades he would have seen the triumph of his principle, but he died at the age of 47. At the end he became insane (and no wonder), but we read with astonishment and anger that he was induced in a friendly way to visit a mental institution where he was forcibly detained and restrained, "confined to a strait jacket and put in a dark room." Nor was his wife allowed to see him next day. He died from septicaemia arising from a septic wound of the finger, but one wonders to what extent his final treatment affected his body's defence mechanisms. The ending is sombre, like the climax of a Greek tragedy.

ZACHARY COPE.

**Immortal Magyar. Semmelweis, Conqueror of Childbed Fever.* By Frank G. Slaughter, M.D. (Pp. 211; illustrated. $3.50.) New York: Henry Schuman. 1950.

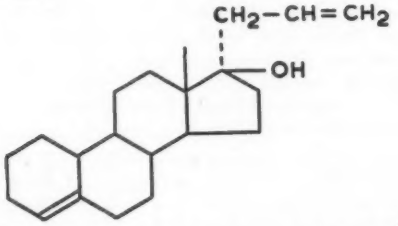
To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in common use.

Allyloestroenol

"Gestanin" (Organon Laboratories).

Chemistry.—The compound is a member of a new series of steroids, the 17-alkylated 3-deoxo-19-nor-testosterones (or oestroenoles). Gestanin is 17α-allyloestr-4-en-17β-ol. Structural formula:



Pharmacology.—In the past few years several orally active synthetic progestogens have become available. Chemically they occupy a position between the natural androgens and oestrogens. Hence not only the progestational effects of such substances have to be studied but also the possibility that they inhibit the gonads, impair pregnancy, and exert androgenic effects. In tests on rabbits allyloestroenol proved to be effective in smaller oral doses than dimethisterone or ethisterone. The compound was also very active in deciduoma tests in mice, and maintained pregnancy in spayed rats. No signs of virilization could be detected in the foetuses obtained in the experiments on maintenance of pregnancy or in castrated male rats, but virilizing effects on the female foetus have been reported when the compound is given in high doses. An inhibitory effect on female and male gonads was found with high doses, but it was weaker than that of norethisterone or methyloestroenolone. No depressant action on adrenocortical function could be demonstrated in rats which had either received a large single dose intraperitoneally or in others which had been treated with subcutaneous doses for ten days.

Therapy.—Allyloestroenol has been tested in patients with: (*a*) Menstrual disturbances (menorrhagia, amenorrhoea, anovular menstruation, true metropathia). Dose: 10–15 mg. daily from day 12 or 19 to day 26 during several cycles. (*b*) Dysmenorrhoea. Dose: 10 mg. daily for several months. (*c*) Premenstrual tension. Dose: 5–10 mg. daily for 3–5 days in each menstrual cycle, usually starting three days before the expected onset of symptoms and ending three days before the period was due. (*d*) Abortion syndrome and threatened abortion. Dose: In cases of recurrent abortion the patients received first 15 mg. daily from day 16 to 26 of the cycle for three months. Those who became pregnant were given a further course of 10 mg. daily for sixteen weeks. The compound proved in most cases to be a satisfactory and well-tolerated oral progestogen.

Side-effects.—Considerable increase of libido in some of the patients treated for premenstrual tension or dysmenorrhoea.

N.H.S. Basic Price.—100 tabs., 52s.

A new health centre in Hong Kong is to be named after the wife of the Colony's Governor, Sir ROBERT BLACK. The Anne Black Health Centre will be built in Hong Kong's heavily populated North Point district, and will cost an estimated £31,250. Situated at the junction of Tsat Tse Mui Road and Healthy Street, it will have three departments: an out-patient department, a maternity ward, and a child health clinic.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Radiological Hazards

SIR,—The Adrian Report confirms that the precautions previously adopted by radiologists have proved fully adequate to protect patient and operator, and liquidate much of the exaggerated dangers alleged by some of our overenthusiastic physicists.

An outstanding omission from the Report, however, is the lack of being strictly precise about protection. For example, the precise lead–rubber equivalent for the protection of the genital organs has not been stressed. Recently I had sent to me a "protective apron." It duly underwent my routine test by *x*-ray examination. Below is a photograph of the result (Fig. 1). The apron is useless for protecting a patient.

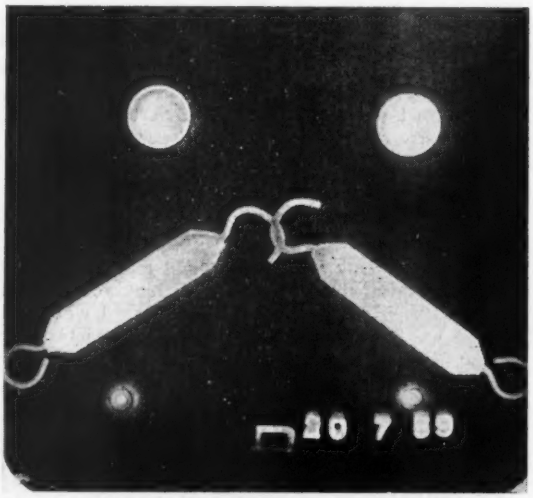


FIG. 1.—Radiograph taken through apron, with springs, coins, and date below the apron showing up clearly.

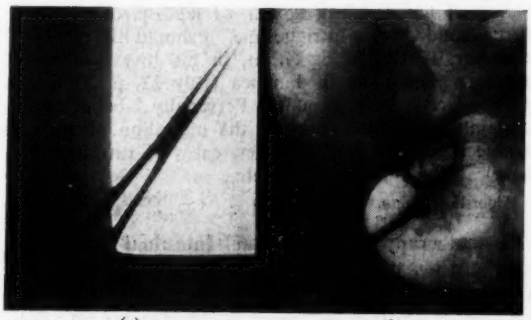
Grave dangers exist in marketing these lead–rubber articles without stamping on the article the lead equivalent employed, and a brief description as to the purpose of its use. The lead equivalent of the apron was only 1.5 mm., whereas at least 2 mm., or preferably 3 mm., would have been safer. The importance of the lead equivalent cannot be overstressed, and while some manufacturers stamp it on their products others do not.

Another important omission was the question of metal cones in radiography. Cones concentrate the beam and no radiation goes outside the cone circle. This is an additional type of protection to the patient and operator, while, in addition, cones produce radiographic detail on the films of a greatly increased quality than those pictures taken without the cones (Fig. 2). Note with cone, the half of the Spencer-Wells forceps shows a sharp image inside the cone but outside the beam is completely shut off.

All walls of an *x*-ray department were *x*-rayed. Sections of the walls showed porous mortar slits and *x* rays were recorded on films on the other side of the wall. Rays passed approximately 15 ft. (4.6 m.) farther into the next room, where hospital staff worked. As *x* rays

can be accumulative, any leakage, however small, should be sealed, and it was. For testing walls the following technique was adopted: 100 kV, 100 mA, 15 seconds exposure made in 5 bursts of 3 seconds with or without filter. Film placed at tube target level on opposite side of wall. Fast film in cassette with fast screens, and 12 in. (30 cm.) × 4 in. (10 cm.)-diameter cone.

Routine screening of opaque meals and enemata is largely wasted effort. Only a small proportion will require screening, such as cases of oedematous, buried, or thrombosed ulcers (gastric and duodenal); abdominal adhesions, mobile "hide and seek" polyps waving about on stalks, and cases of visceroptosis with a bowel



(*a*) (*b*)

FIG. 2.—(*a*) Without cone; (*b*) with cone.

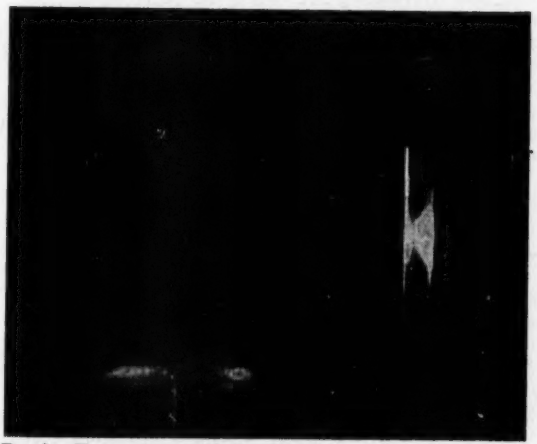


FIG. 3.—*X* rays photographed penetrating mortar spaces between bricks.

flopping in the pelvic cavity and obscuring a small growth. Take the films first and screen after if it is required. This advance has been achieved by the startling improvement in the modern high-speed films with intensified rapid screens, resulting in the film recording much more accurate detail than the more imperfect screen and eye.

One last criticism is offered of the Report, and that is the composition of the Adrian Committee, where there was a distinct minority of radiologists. As we have many first-class experts throughout this country who are well versed in *x*-ray matters and protection, why employ so many surgeons and physicians? — I am, etc.,

London W.1. NORMAN P. HENDERSON.

REFERENCE

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Hospital and Medical School Design

SIR,—It is perhaps rash to comment on your short report (August 19, p. 512) of the symposium in Dundee on hospital and medical school design, but it is only too clear from the sketch plans that ward planning shows little sense of direction or progress. Two main points worry me: firstly, the acceptance of the large ward round of about 20 students as a guiding principle (St. Thomas's Hospital), and, secondly, the logic in the provision of single rooms. As regards the first point, the Minister of Health has asked us all to lead in a more humane approach to the patient. Taking a crowd of students round a bed with a discourse or discussion that all can hear (including the patients) is not the way to forward these aims or teach students anything but our own insensitivity.

As regards single wards, it is impossible to read from these plans the exact purpose of these rooms. At St. Thomas's they are few (14%), and are presumably for dying or noisy patients. At Ninewells, Dundee, it is suggested that flexibility of admission of men and women is achieved by their use. Surely it's time to consider the necessity of single-bedded wards in terms of progressive nursing care, providing a suite of rooms with maximum audio-visual communication between nurses and patients. In this case the nurses' station must be appropriately sited in relation to these rooms, the W.C.s in each room be placed on the outer wall, the wall and door in the corridor be amply glazed, and each room be provided with technical equipment (oxygen, suction, etc.).[1] It is to be understood that the first stage of progressive nursing is intensive nursing care—this is logical and probably economical—in which case the rooms are intended for the nursing of all the very ill patients who need rest, quiet, and constant supervision or isolation.

These desiderata cannot be achieved in open wards, where the use of curtains immediately obstructs the visibility of many beds. The argument is given in more detail in my article in *The Architects' Journal*.[2] Intensive nursing care should not be considered in isolation, and we do not yet possess sufficient information about the average loading in wards of patients requiring this level of care. Such information should be easy to obtain, and might well justify Dame Janet Vaughan's suggestion (August 19, p. 513) that more attention be given to hostel type of accommodation.

I will not occupy your space with detailed criticism, but one must notice the bottlenecks in the St. Thomas's plan of less than 5 ft. (1.5 m.) entrances to the 12-bed groups. While the Dundee plan does achieve a relatively much shorter perimeter and larger internal space per bed, a much tidier design could have been achieved with closed 4-bedded rooms at a possible loss of 4 beds, thereby avoiding the open 18-bed ward in deep clusters of 6. One must express the keenest disappointment at the slow rate of development in our hospital architecture.—I am, etc.,

London W.1. HUGH GAINSBOROUGH.

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Diabetes, Neurogenous Deafness, and Retinal Degeneration

SIR,—Diabetes mellitus, neurogenous deafness, pigmentary degeneration of the retina, and obesity have recently been reported by Alström *et al.*[1] in three members of two interrelated families. They consider the syndrome to be a distinct genetic and clinical entity, not hitherto described. They also draw attention to the similarity of the Laurence–Moon–Bardet–Biedl syndrome to the syndrome they describe. Variants of the former syndrome are well recognized and include neurogenous deafness; they are due to pleiotropic manifestations of a single recessive gene. Alström and his colleagues suggest that the syndrome they have described is a homozygous manifestation of a recessive gene mutation at a different locus to that responsible for the Laurence–Moon–Bardet–Biedl syndrome. This conclusion is reached after a thorough genetic analysis of the families of the patients they describe.

The following case seems worthy of reporting in view of the similarity to those described by Alström *et al.*

The patient is an unmarried man, aged 47 years, resident at a school for the blind. He is an orphan with no known relatives. He maintains he has been deaf since early childhood. The first reliable information relates to his training at the Royal School for the Deaf in Manchester, where he had been a pupil from 9 to 16. At the time of leaving he was partially deaf and had a very limited vocabulary, but was able to lip read. His sight and intelligence were considered normal. Visual deterioration began at about the age of 30 and progressed, until at 43 years he was registered as a partially sighted person. Severe diabetes mellitus, with an acute onset, developed when he was 44. Under the supervision of the diabetic clinic at King's College Hospital the diabetic state has been well controlled with insulin.

On examination he is of short, asthenic physique. Height 5 ft. 4 in. (1.6 m.); weight 133 lb. (60.4 kg.). His speech is limited to a few simple words and his main method of communication is by finger spelling. He would be assessed of average intelligence. He has severe, bilateral, perceptive-type deafness due to changes in or lack of development in the hearing end-organ (Mr. Terence Cawthorne). His visual acuity is 6/24 in both eyes, whilst the visual fields are contracted. He was seen by an ophthalmologist (Mr. L. H. Savin), who considered that the visual defect was due to gyrate atrophy of the choroid. Ophthalmoscopy showed choroidal atrophy in the fundus periphery with scattered retinal pigment and bilateral optic atrophy of the retinal type. The condition is similar to retinitis pigmentosa. There were no other abnormal neurological findings. Other systems were normal.

Investigations: Hb 83%, W.B.C. 8,200 c.mm. Wassermann reaction in blood was negative. Liver function was normal. Apart from variable small quantities of sugar in the urine there were no abnormal constituents. Skull *x*-ray was normal. Routine scalp E.E.G. showed no significant abnormalities.

In the three cases described by Alström *et al.*[1] the pattern of development of the syndrome was similar. Visual deterioration progressed up to the age of 7 to 8 years, whilst neurogenous deafness occurred in adolescence. Diabetes mellitus developed in adolescence in two cases, whilst the third had an abnormal glucose tolerance test of "diabetic type." General obesity was present in all three cases. The case reported here was not obese and the visual deterioration and diabetes mellitus occurred at a later age than in Alström's cases. In spite of these differences, this case does resemble the syndrome described by Alström *et al.*, and gives some slight support to his claim that the syndrome is a clinical entity. No contributions to Alström's genetic hypothesis can be made, owing to the absence of a family history in this patient. In view of the small number of cases as yet described, the claim to have a new clinical and genetic entity would seem premature. Reporting of further cases with genetic studies may help establish this claim.—I am, etc.,

The Maudsley Hospital, London S.E.5. JOHN JOHNSON.

REFERENCE

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Atypical Pneumonia in British Caribbean

SIR,—I am a crank so far as leptospirosis is concerned, and Q fever intrigues me. I should like to know, however, if Dr. L. S. Grant, in his investigation of atypical pneumonia in Jamaica (July 22, p. 238), has taken *Ascaris* into account. Personally I believe that, certainly in children abroad, the migration of *Ascaris* larvae accounts for a good few cases of transient and atypical pneumonia.—I am, etc.,

Aldershot, Hants. NED CURRAN.

Chemotherapy of Urinary and Intestinal Infections

SIR,—I would comment on two statements in the letter of Dr. G. A. Stanton (August 19, p. 519). Firstly, his implication that pathogens in a lumen cannot affect the patient. Surely by their absorbed products they can, and by clearing the lumen the relief of systemic effects is often obtained. Mandelic acid and the anthelmintics still have their place in the treatment of lumens. However, should not the diluent effect of a "fluids + +" regimen be taken into account in urinary infections, since penicillin at least seems to do its work at peak concentrations? "The textbooks and the medical schools" (Dr. Stanton's phrase) stand indicted.

Secondly, he dismisses the "intestinal sulphonamides." "We realize," he writes, that "the absorbed portion (about 25%) was the active portion." My impression in treating diarrhoea in the tropics was that: (1) Succinyl sulphathiazole was often more effective than sulphaguanidine, yet it is only 5% absorbed—i.e., 0.15 g. absorbed out of a six-hourly dose of 3 g. This makes it a powerful agent, if Dr. Stanton's contention is correct. (2) Streptomycin was more effective than either drug, and yet is not significantly absorbed. The systemic effects of intestinal pathogens may warrant systemic therapy, but many intestinal infections seem to respond to local agents.—I am, etc.,

Crookham, Hants. J. S. WRIGHT.

⁂ Comment on Dr. Stanton's observations was made last week (p. 574) in an annotation entitled "Local or Systemic Action?"—ED., *B.M.J.*

Subjective Assessment in Clinical Research

SIR,—Drs. C. M. Fletcher and C. M. Tinker (July 22, p. 245) have listed some of the problems they would like to investigate by means of questionaries, but suggest that it would be difficult to apply our technique. In our letter (June 24, p. 1828) we showed how we would deal with the problem of estimating the frequency of early-morning cough, and the problems mentioned offer no greater difficulty. For example, the question of the varying frequency of cough with seasons can be treated by using separate lines, one for each season. The patient marks each line according to the method already described.

Our claim is that by this method we can obtain all that can be obtained by the use of the "Yes/No" method, but with greater precision. It appears from their statement, "For these purposes the simple Yes/No answer seems to work pretty well," that Drs. Fletcher and Tinker are willing to accept a low level of accuracy. Surely it is much sounder to gather data in the most accurate way practical, even though some may be discarded later. Drs. Fletcher and Tinker admit that their technique breaks down in "some borderline cases which are arbitrarily classed as negative," but when it is the *patient* who is left to resolve any ambiguities it is impossible to estimate how many decisions are borderline, so the amount of negative bias is unknown.

Drs. Fletcher and Tinker suggest that their method is validated by a comparison of the results of two independent surveys on the "relationship between answers to questions and winter sputum volumes in two male populations" (Table VIII, May 27, p. 1495). By their technique the patient has three alternatives, "Not at all," "Part of the time," and "All the time." It is apparent that the middle category contains all but the two extremes and so is much wider than the other two categories. Hence it is not surprising that the results of the two independent surveys show no disagreement for the two extreme categories but show a significant ($P=0.05$) *disagreement* for the middle category. Had a continuous scale been used in place of the three categories by asking the question, "How much of the time do you bring up sputum?" the results of the two surveys could have been compared with greater accuracy.

With regard to the question of fallible memories, we fully recognize the dangers of retrospective surveys, but consider that any such objection applies equally to all questionary techniques. In the one investigation we have conducted in which it has been possible to estimate the importance of distortion due to the time elapsed between the events and their recall, it was found to be negligible compared with the main effects in which we were interested. However, there can be no general solution to this problem; it needs to be examined afresh in each investigation.—We are, etc.,

J. L. GEDYE.
R. C. B. AITKEN.
HELEN M. FERRES.

R.A.F. Institute of Aviation Medicine,
Farnborough, Hants.

Congenital Dislocation of the Hip

SIR,—Mr. Gavin C. Gordon's letter on congenital dislocation of the hip (July 29, p. 311) raises a point of very considerable interest, but first let me point out an error. He states, "All newborn infants have slack or loose hips to some extent." This is not correct. Out of 8,200 children examined in the first week of life only 113 had lax hips, in all the others the hips were absolutely stable.

Mr. Gordon then goes on to say "many cases of congenital dislocation of the hip do not make their appearance until the child begins to walk. . . ." There is of course a difference in being present and making their appearance. Can Mr. Gordon, or anyone else, *prove* that these hips had not been dislocated for a long time before they were found? Out of these 8,200 children 5,865 are now 1 year old, and so far not a single child among those who started with normal hips has subsequently developed any abnormality. It would therefore seem likely that if congenital dislocation makes its appearance after birth such an event must be extremely rare.

I agree with Mr. Gordon when he says that "clunking" or "clonking" can frequently be elicited in newborn children, and that the majority of these recover spontaneously, but I feel that there is a very strong case for supposing that these lax hips also include nearly all, if not all, the congenital dislocations. I am well aware of the view that congenital dislocation can occur after birth either when the legs are extended or when the child first walks, but is this a proven point, or is it a surviving conception and belief of ancient medicine?—I am, etc.,

Salford. T. G. BARLOW.

SIR,—It was good to read Mr. Norman Capener's letter (July 1, p. 47) and to see that the work of von Rosen and his colleagues in Malmo was being appreciated in Britain.

I thought that your readers might like to see the way the Chinese in Hong Kong treat their children from birth. The picture shows the method of carrying the infants in Hong Kong, which is both practical and convenient, the mother often working with the child happily asleep on the back.

It may interest you to know that in the past ten years we have seen ten cases of congenital dislocation of the hip among a population of three million odd, and that in each case the baby had not been carried on the mother's back, but had been brought up in Western style with bulky napkins and the legs pulled down and contained within blankets in a pram and cot.—I am, etc.,

Orthopaedic Department, A. R. HODGSON.
University of Hong Kong.

Skin Disease in Africa

SIR,—I write this letter in reply to Dr. James Marshall's inquiry regarding skin disease in Africa (May 27, p. 1544).

I have collected the following common skin diseases one sees in Ghana: (1) onchodermatitis, which manifests itself as (*a*) acute urticarial reaction, (*b*) pruritus, (*c*) generalized septic dermatitis, (*d*) generalized oval plaques brownish-purple in colour, (*e*) patches of depigmentation; (2) tinea (all forms): *T. corporis, T. cruris, T. capitis, T. pedis*; (3) dermatitis (various); (4) furunculosis; (5) impetigo; (6) malnutrition with skin manifestations (avitaminosis and kwashiorkor could be included here); (7) urticaria; (8) prickly heat; (9) leprosy; (10) yaws, post-yaws "ichthyosis," plantar hyperkeratosis, pintoid yaws. Florid yaws, either primary or secondary, is a rarity.

The majority of patients seen are Africans. The expatriates (Europeans and Asiatics) and their families are less prone to onchocerciasis, leprosy, and yaws as they are not often exposed to infection—for example, bites of *Simulium* flies, contact with cases of leprosy or yaws. Their nutritional status is better than that of the African and so nutritional skin diseases are not often seen in them. The other skin diseases show no marked racial difference in incidence.

There is a high incidence of onchocerciasis in people from the northern territories of Ghana who have migrated to the south. I have found a high percentage of positive skin snips showing onchocerca larvae in Frafras, Moshies, etc., who have settled in this area from the northern provinces.—I am, etc.,

Central Hospital, Kumasi, Ghana. P. RABINDRAN.

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[2] Trowell, H. C., and Jelliffe, D. B., *Diseases of Children in the Subtropics and Tropics*, 1958. Arnold, London.

Examiners for Nurses' Finals

SIR,—I am writing to ask you to give prominence in your journal to changes about to be introduced by the General Nursing Council for England and Wales in their final examination for registration on the general part of the Register of Nurses. The examination includes written, practical, and oral tests, of which the combined practical and oral examination is conducted entirely by nurse examiners, and my only concern with it here is to note that the difficulty of enlisting a sufficent number of medical examiners interested in nursing education was one factor leading to the abandonment in 1950 of separate oral tests conducted by members of the medical profession.

The written part of the examination has hitherto consisted of three papers. In theory one paper is entirely confined to nursing, the other two based on medicine and surgery respectively as applied to nursing. In practice the distinction between these papers is hardly tenable, and for a long time it has been felt that nursing education should be directed towards eliminating such artificial divisions.

The present educational policy of the General Nursing Council recommends that an elementary course of lectures in medicine and surgery be given at the end of the first or beginning of the second year of the student nurse's training, followed by a more specialized course later in the second or early in the third year. It is hoped that the subjects will be integrated with each other as far as possible, as well as with the teaching of actual nursing procedures and care of the patient, and ancillary matters such as dietetics. The occasional panel discussion would be ideal; sister tutor, dietitian, physician, and surgeon could, for example, co-operate advantageously in the teaching on peptic ulcer. Such a system is felt to be a great improvement on the traditional complete course of lectures in medicine or surgery, each given at an arbitrary period in the nurse's training, sometimes without correlation with her practical experience.

The changes being introduced into the written part of the final examination for State registration will embody these principles in two general papers set by an examining board of two nurse-tutors, one physician, and one surgeon, and corrected by a panel of examiners drawn from both nursing and medical professions. One of the main purposes of this letter is to recruit additional examiners from the medical profession to the existing panel. This at present is comprised largely of consultant physicians and surgeons, but with the more general nature of the papers in future the General Nursing Council would be glad to receive applications from a wider field. An interest in the teaching and training of nurses is the qualification most desired, and those who already participate in this training by giving lectures are of course particularly suitable. In all a medical panel of 170 is desirable, and those interested are asked to apply to the Registrar, General Nursing Council for England and Wales, P.O. Box 803, 23 Portland Place, London W.1.

While putting this matter before the profession on behalf of the General Nursing Council I would like to take the opportunity of adding a comment of my own. I would point out that, fortuitously, these changes should to some extent mitigate the criticisms of the examination, not always well informed, that have appeared in the medical press of recent years. I would add, however, that the majority of nurses are quite able to answer the questions which have been criticized as too academic. Perhaps some of these critics will apply for an examinership and, if appointed, change their view. In an age when the general public is educated in electroencephalography, in the constitution and behaviour of deoxyribonucleic acid, in the heart–lung machine, and stereotactic operations for Parkinsonism, to quote but a few, the nurse cannot be denied the knowledge she requires—for example, on the rectification of electrolytes, a matter she is handling daily. Indeed, the nurse will not be denied, and that is the gist of the matter. I can none the less assure the critics that the practical nursing part of the examination carries the greatest weight and the largest proportion of marks, while no nurse is ever failed for want of abstruse academic knowledge. Moreover, for those often good practical nurses who find difficulty in answering a written paper there is the position of State Enrolled Nurse (S.E.N.), which is slowly coming into its own.—I am, etc.,

London W.1. M. M. C. LOUDEN, Chairman of Examining Board, G.N.C. Final General Examination.

⁂ Comment on Miss Louden's letter appears at p. 635.—ED., *B.M.J.*

Fainting in the Dental Chair

SIR,—Since many people seem reluctant to acknowledge the possibility that fainting during induction of anaesthesia in the dental chair may occur, I should like to report a case in the hope of encouraging more careful observation of the patient at this critical time, so that disaster may be more often averted.

The patient was a fit young man in his twenties who had come for extractions. He had had nothing by mouth for 14 hours and was not clinically anaemic. He appeared to be a little more nervous than most patients are when faced with a dental anaesthetic. He was positioned in the chair, and the Walton machine adjusted to give 100% nitrous oxide at about 3 lb./sq. in. (0.2 kg./sq. cm.) pressure. Just as the nose-piece was being applied, he complained that he felt slightly sick. The mask was removed, and after about two minutes he said he felt better. Induction was begun again as before, and after about ten breaths of 100% nitrous oxide the patient began to breathe irregularly and to retch. At the same time he was noticed to be pale and to have beads of sweat on his forehead. His radial pulse was sought for (previously easily palpable), but was absent. He was unconscious, his lips were slightly cyanosed, but no jactitations occurred. The chair was then immediately tipped back so that his body was horizontal, and 100% oxygen was administered. His radial pulse immediately reappeared, strong and at a rate of about 65/minute. He recovered consciousness as though from a normal nitrous oxide anaesthetic, but remained pale and sweaty for a few minutes.

About half an hour later he was again anaesthetized, using a 50:50 mixture of cyclopropane and oxygen (without premedication) and in the semi-prone position, without incident.

In this patient fainting was easily recognized, but this is not always so, and it may pass unnoticed even by experienced practitioners who are specifically watching for this complication. Nevertheless, careful observation should detect, at the time, most cases of fainting in the dental chair. In this case there were three possible aetiological factors—namely, an excessive period of starvation, nervousness, and induction with pure nitrous oxide in the sitting position, each of which may have contributed its quota to the final result.—I am, etc.,

Department of Anaesthetics, St. Thomas' Hospital, London S.E.1. R. M. M. FORDHAM.

Nitrous Oxide in Dentistry

SIR,—On my return from holiday I found the letters by Dr. M. P. Coplans (June 3, p. 1607, and July 22, p. 246) made stimulating reading. However, I find some of his arguments a little difficult to follow. With regard to his children, when crying for their bottle, are they not presumably making use of their seven millilitres of available cerebral oxygen, and are they likely to hold their breath for more than one minute of time? He next states he is very anxious that no oxygen lack shall occur due to mishandling of patients, but maintains that deliberate withholding of oxygen is completely safe. Does the body react differently when oxygen lack is due to accident rather than to design? One would not dispute with him that, with mishandling, CO_2-accumulation will add its own dangers, but, with a fully patent airway, does Dr. Coplans seriously contend that there can be no after-effects from oxygen lack?

It has been stated by Barcroft that a short period of oxygen lack followed by full oxygenation is probably harmless. Therefore nitrous oxide with no oxygen, given to a stage of unconsciousness sufficient for a "quick snatch," and followed immediately by normal breathing with the mask removed, may be harmless, and many, including myself, have often survived this insult with, I hope, no deleterious results. But difficult or multiple dental extractions can take, say, up to twenty minutes. Does Dr. Coplans still maintain that to keep a patient suboxygenated for this length of time is likely to benefit that patient's health? Has he ever personally undergone such an experience? I have, and can assure him that the after-effects, if not serious, are certainly unpleasant. Also, I have in my own unregenerate hypoxic days had to give subsequent treatment to at least two of my own patients whom I had "anaesthetized" à la Coplans.

He also disapproves of using other agents as supplementation because he is not so convinced of their safety as he is of the harmlessness of oxygen lack. The necessity of ensuring immobility (not amnesia and analgesia) in the occasional refractory case implies such a small amount of such supplementation that it cannot detract from the overall advantages of nitrous oxide without oxygen restriction. Anaesthetic authorities are unanimously of the opinion that oxygen lack can be considered almost the greatest hazard in anaesthesia, and most anaesthetists must, alas, at some time, have seen the scales tipped against a poor risk patient when such an accident has occurred. Dr. Coplans affirms that his patients subjected to "controlled" hypoxia do not die or go mad. He has been fortunate. His championship of oxygen restriction could be understood if it was proved that by no other means could nitrous oxide anaesthesia be produced or maintained. Klock and I,[1-3] in well over ten thousand cases, have proved that for "gas in the chair" oxygen restriction is unnecessary. As it is also, at the very least, undesirable, why persist in its advocacy?—I am, etc.,

General, Eye, and Children's Hospital, Cheltenham. ARTHUR TOM.

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Blood Transfusion for Mass Casualties

SIR,—Dr. R. A. Zeitlin's explanation (August 12, p. 455) of his phrase, "the two common Caucasian blood groups O and A," shows that he meant the two blood groups O and A, common in Caucasoids. He evidently was not suggesting that the difference lies in the blood groups themselves, but only in their distribution.

However, his various definitions of "Caucasoid" raise further difficulties. The standard work on blood-group distributions[1] shows certain "White" European populations having less than the required 80% of O and A—namely, in Hungary, Jugoslavia, Poland, Estonia, Latvia, and Russia. Eire, with twice as much O as A, is hardly "in roughly equal proportions."

Some of the populations in the Caucasus itself are not "Caucasoid." Going further east, the irrelevance of Dr. Zeitlin's term "Indo-Europeans" appears when all Persia and almost all India—including Brahman groups—have that rising B which, Dr. Zeitlin tells us, characterizes the Negroid and Mongoloid races. On the other hand, the Maori of New Zealand and some of the South Sea Islanders have "Caucasoid" percentages.

My reasons for going into this detail are two: that all these peoples must be considered in arranging for "mass casualties" in any future war, and, more serious, that erroneous concepts of the meaning of synonyms of "Caucasoid" have caused one war and may well, in South Africa, cause another.—I am, etc.,

Summerfield Hospital, Birmingham 18. ROBERT J. HETHERINGTON.

REFERENCE

[1] Mourant, A. E., Kobeć, A. C., and Domaniewska-Sobczak, K., *The ABO Blood Groups*, 1958. Blackwell, Oxford.

Early Maturing and Larger Children

SIR,—As a contrast to your leading article on early maturing and larger children (August 19, p. 502) I suggest an editorial on slow development and late maturing children of long-lived families.

My experience and observation has been that in long-lived families (British) the children tend to be up to one or even two years behind their real age in their physical and mental age. I realize that to argue from the particular to the general is not of great value, but in my own case and in that of my family, and three or four other families which I have noted, development from childhood to an adult stage has been definitely one to two years behind actual age. In my own case, when I went up to the varsity at 18 years of age I was 7 st. 8 lb. (48.1 kg.) and 5 ft. 2 in. (1.5 m.). I grew until I was 25 to 5 ft. 11 in. (1.8 m.) and have been

12 st. 12 lb. (81.6 kg.) for years. Incidentally, I have played games beyond the normal ages: rugger up to 46, hockey to 63, and cricket to present age.

My four children (two boys, two girls; boys seem to lag more than girls) have been the same. In some ways this was a great handicap at and beyond the end of school life when trying to compete for scholarships, etc. None of us got scholarships, but all finally got firsts or seconds in university finals. I have observed the same in children of three other long-lived families in which the parents or/and grandparents lived well into the eighties and nineties. I suggest that this might be a subject for research and comment in an editorial. —I am, etc.,

Chulmleigh, N. Devon. TREFFRY O. THOMPSON.

Vagotomy for Peptic Ulcer

SIR,—May I make a plea that Mr. Harold Burge clarifies his prose? In his letter (August 12, p. 456) he writes, "Let us be essentially practical and find the proved recurrence rate of vagotomy . . ." One can only assume that this must mean the recurrence rate of chronic peptic ulceration following vagotomy, and, having assumed this, one wonders whether he refers to chronic recurrent duodenal ulcer or chronic gastro-jejunal ulcer arising *de novo* following gastro-jejunostomy. One then proceeds to wonder how the true incidence of these lesions is to be assessed. Is it to be on clinical features, on radiological appearances, or on gastroscopy? I submit that none of these methods is diagnostically accurate enough to arrive at the truth of the matter, and the probability of false conclusions is therefore considerable.—I am, etc.,

London N.21. GARDEN HENDRY.

Fusion of Labia Minora

SIR,—Dr. C. J. Carr, in recording his interesting case of adherent labia minora in a parous woman (July 29, p. 314), asks for enlightenment. I have seen a number of cases of adherent labia minora in young children. From the circumstances, I have regarded the condition as inflammatory in origin. All the cases were sent to me because they were suffering from disturbances of micturition of one kind or another, otherwise they probably would never have reached me.

Under an anaesthetic, I have found that the adherent parts separate quite readily by applying tension on the adhesion with gauze-covered fingers. Post-operative separation is satisfactorily maintained with a simple lanoline dressing.—I am, etc.,

London W.1. H. P. WINSBURY-WHITE.

Intraperitoneal Haemorrhage from Fibroids

SIR,—Intraperitoneal haemorrhage from fibromyoma of the uterus gives rise to acute emergency at times. The complication is unusually rare.[1] Two cases are here reported.

Case 1.—A 19-year-old primigravida was admitted to the Rao J. N. Roy Hospital in June, 1959. She had marked toxaemia of pregnancy at 38 weeks. On admission she complained of vague abdominal pain. Her blood-pressure was 170/110, there was marked oedema of the legs, and the urine was loaded with albumin. The height of the fundus corresponded with the period of amenorrhoea. The baby was presenting cephalically and the foetal heart was not heard with certainty. A few hours after admission it became apparent that the mother's pulse rate was gradually rising, and she became pale. The blood-pressure fell to 140/100. The abdomen was distended and had developed generalized rigidity and tenderness. On palpation the uterine outline was no longer definite. The foetal heart could not be heard any more. The cervix was tubular and closed, and the pouch of Douglas was tender. The child was presenting by vertex and was at the brim. A diagnosis of severe accidental haemorrhage, akin to couvelaire uterus, was made, and laparotomy was performed. The abdomen was full of blood. The baby was delivered quickly by caesarean section, but was dead. The placenta was extracted and there was no evidence of accidental haemorrhage. On the posterolateral surface of the uterus there was a small fibroid, about 2 in. by 2 in. (5 cm. by 5 cm.). The fibroid was very soft and had a rent on its surface, where a vessel was spurting. There was also oozing from all over its surface. Myomectomy was done and the raw area was covered. Histology showed red degeneration. The patient made an uneventful recovery.

Case 2.—A 32-year-old mother of three children was admitted to hospital in August, 1959, in a collapsed state with severe abdominal pain and slight vaginal bleeding. Her period was overdue by one week. Her blood-pressure was 84/60. The abdomen was rigid, more so in the lower abdomen. Pelvic examination failed to reveal any mass, but was extremely painful. The uterus could not be felt. A provisional diagnosis of ruptured ectopic gestation was made, and laparotomy was performed. The abdomen was full of blood. The tubes and ovaries were normal. A fibroid (3 in. by 3 in.—7.5 cm. by 7.5 cm.) on the anterior surface of the uterus was partly detached from its bed, leaving a small cavity as if someone had been trying to enucleate it. The torn area was bleeding freely. Myomectomy was done and the raw area was covered up. The patient recovered uneventfully.

Marrow[2] has reported intraperitoneal haemorrhage from spontaneous rupture of a varicose vein of the uterus during pregnancy where there was no fibroid. Recently Bigby[3] and Badaway[1] have reported two cases similar to our own. It appears, therefore, that intraperitoneal haemorrhage from the ruptured uterine veins, whether over a fibroid or from varicosity, may precipitate an acute emergency. Trauma, increased intra-abdominal pressure, and vascular congestion during menstruation have all been blamed as precipitating factors. In one of my cases red degeneration of the fibroid together with toxaemia of pregnancy precipitated the crisis. The cause of bleeding in the other case is difficult to explain. It seems likely that the fibroid was intramural to start with, and that the uterus, treating it as a foreign body, was trying to expel it. When the fibroid was partly detached from its bed free intraperitoneal bleeding occurred, giving rise to shock and peritoneal irritation.

The treatment is myomectomy in most cases, as these patients are gravely ill and also comparatively young.

I am grateful to the C.M.O.H. and the D.M.O., Murshidabad, for their kind permission to use the case records.

—I am, etc.,

Rao J. N. Roy Hospital, Murshidabad, West Bengal, India. PROBHAT KUMAR CHOUDHURI.

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Betamethasone

SIR,—Dr. R. O. Gillhespy's experiences (August 12, p. 454) with the use of betamethasone in rheumatoid arthritis are at considerable variance with those which

we are about to report in a series of 60 patients. The most startling discrepancy is that a third of his patients failed to show a satisfactory anti-inflammatory effect. By contrast, only one of our 60 patients failed to respond demonstrably, and few required more than 1.5 mg. per day. It would, therefore, be interesting to know the *individual* dosages given to Dr. Gillhespy's 12 patients who failed to respond. At the end of a year we have classified 41 of the patients as being either asymptomatic or satisfactorily controlled.

We do not claim that the incidence of *inevitable* side-effects is significantly different with betamethasone than with previous steroids, but, since by far the most frequent of the reported side-effects in both series refer to facial mooning and flushing, the figure given for "total side-effects" becomes unrealistic, since we believe that such aesthetic inconveniences are a reasonable price for a severely ill patient to have to pay to achieve comfort, and it is wrong to give steroids to any patient unless he has severe and progressive arthritis. Of the other side-effects mentioned, most of the patients who gained weight in our series were satisfactorily controlled by a reducing diet often supplemented by anorexic drugs. Of the 27 cases in which direct comparisons were made, only three felt better with the steroids they had previously been taking.

We agree with Dr. Gillhespy that it would be convenient if a simple tablet-for-tablet substitution could be made when switching a patient from one steroid to another, and our postulated dose ratio of 1 mg. betamethasone: 8 mg. prednisolone suggests that the present size of betamethasone tablets (0.5 mg.) is rather low for the purpose. However, there is a wide range of individual response in this ratio, and the important thing is to have tablets of small denomination so that subtle dose changes can easily be made.

On the positive side, we have been struck by the fact that steroid "tolerance" has not developed in any patient on maintenance betamethasone. This contrasts markedly with our experience with earlier steroids and is of itself a justification for a careful clinical assessment of new preparations with modifications of the steroid nucleus. While betamethasone certainly does not represent the ultimate goal in this respect, it does appear to be a worth-while advance, and we disagree with Dr. Gillhespy when he belittles the importance of significant price reductions in equipotent products.—We are, etc.,

The Prince of Wales's General Hospital, London N.15. JOHN H. GLYN. DAVID B. FOX.

Childhood Obesity

SIR,—The article by Drs. June K. Lloyd, O. H. Wolff, and W. S. Whelen (July 15, p. 145) makes an interesting addition to the annals of the overweight. One would like to hear more about these 98 children. How was the diagnosis of "simple obesity" made? One wonders especially about the criteria for a boy of 1 year and 4 months and a girl of 1 year and 10 months. Why did the majority cease to attend regularly after the first year of treatment? Was there any relationship between weight-reduction and regularity of attendance? One would also like to know how these children came to attend a clinic for overweight children. Were most referred for their overweight condition by family or public health practitioners? Or were they selected for treatment from among the children attending the hospital? Was financial help given for maintenance of the special diets? Most important of all might be the interpretation given to the parents and children of the aim of weight-reduction. Does one advise a child to become slimmer for his looks, his convenience, or his health and longevity? If we fail in our attempts to reduce him to "normal" we may leave him to heavier doubts and difficulties than if we had never begun treatment.

A person's shape, a child's shape, is his own. The attempt of others to alter it, for whatever reason, has significance for the overweight subject, and also in the case of a child for the parent. The co-authors of this article are no doubt familiar with the long-term studies of the fat child by Bruch,[1] who found that a fairly accurate prediction of the future course could be made from a detailed history of the physical and emotional development and the family relationships. She also observed that in some cases therapeutic interference, particularly dietary restriction, became the focal point of serious emotional problems. Her discussion of psychotic development in some of these cases is very helpful to the rest of us who are more engaged with height-and-weight tables, removing children's socks, and pills to reduce appetite.

It is well known that a fair proportion of fat overweight children will lose their excess weight without any dieting or drugs. This is one reason for many parental hopes that the child "will grow out of it." The problem then becomes one of selection for treatment. Here the clinical descriptions of Simpson[2] are of the greatest assistance. If one can develop ability in selecting the fat children who will resolve their overweight problem without any treatment, one will reach the heterodox conclusion that better results are obtained in the untreated than in those who receive "energetic treatment."

One feels grateful to Drs. Lloyd, Wolff, and Whelen for their report. But many more studies are required before we can decide, as we look at each fat child, the answers to the following questions: (1) Is this child too fat? (2) If so, why? (3) Should the weight be reduced? (4) If so, can it be done with permanent benefit to the child?—I am, etc.,

Vancouver 8, B.C., Canada. J. M. MACLENNAN.

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Dr. Albert Schweitzer

SIR,—Your Association may be interested in a tribute to Dr. Schweitzer with medical overtones that illustrates vividly the acute mind that has achieved such eminence.

Having followed Schweitzerana for many years, when in Johannesburg recently I called on the chemist who there supplies his hospital with certain drugs. Chatting about the Grand Old Man, this chemist remarked: "Drugs are my graduation subject. I am a young man. Yet when I call on him, talk about any new drug, he always knows all about it, knows its usage, and is quite fully informed in this field. However does he do it, and at his age?"

Two other tributes may justify your space. A dentist chanced to speak of coffee cultures; at once Schweitzer asked, "Which coffee?" mentioning three botanical varieties; he also added where the varieties grew, and between which altitudes.

The nurses and doctors at Lambarene Hospital had planned, impromptu, a dinner festival. Fun and

laughter were the order of the evening. When Schweitzer entered he caught the spirit of the surprise, ordered butter for that evening (a delicacy there), joined in the fun, one item of which was that he decided on a friendly bet between members of the staff on champagne. His verdict would determine the winner. Right off the cuff, when asked, he gave a list of vineyards, gave some special years of fine vintage in some of them, with specialized details concerning champagne. His brain is so precise, so systematic, that it appears as if all he ever read is at once ready for use.—I am, etc.,

MAGNUS RATTER,
Minister,
All Souls' Unitarian Church.

London N.W.11.

Taking an Infant's Temperature

SIR,—I thought I might pass on some information for any of your readers who have found it as difficult as I have to take children's temperatures. Having struggled with my small son to hold a thermometer in either the groin or the axilla, because I do not like putting it in his mouth and he does not like having it put in his rectum, in desperation I put him on the pot while I regained strength for another attack. It then occurred to me that while he was thus enthroned, playing with toys, it would be worth putting the thermometer in the groin, as the baby was accustomed to having his hip flexed when obeying Nature's calls.

I am glad to say that in this position he was too engrossed to be worried about a thermometer, and it remained in his groin as long as I chose.—I am, etc.,

M. N. COX.

London N.W.9.

Lolly Rash?

SIR,—During the particularly hot summer of 1955 a similar rash to that described by Dr. Alun Lloyd-James (August 19, p. 525) was seen upon many of the village children. Its appearance was similar to lichen urticatus, and its cause was traced to a cheap, orange, iced lollipop being sold locally. Antihistamines were effective, but it was a more economic proposition to suggest strawberry instead of orange-flavoured lollipops for future delight. Now that more wholesome and exotic lollipops are being marketed this rash is seen only occasionally.

Later in that same year about 50 children were seen with an irritating, raised, punctate, erythematous rash of the hands, forearms, and elbows, and also upon one or other cheek from secondary contact. All these children had been competing to see which of them could collect the most caterpillars of the common cabbage butterfly. This condition has been described as a rarity and single cases can certainly be puzzling.—I am, etc.,

KENNETH C. EASTON.

Catterick,
Richmond, Yorkshire.

SIR,—I was interested to read Dr. Alun Lloyd-James's letter on "Lolly Rash?" (August 19, p. 525). These ices appear to be a common aetiological factor in childhood allergic reactions, so much so that I make it a stock question when confronted with this condition. Antihistamines readily cure the complaint. One wonders whether the manufacturers will investigate the contents of their lollies, especially the dyes used, now that this has been brought to light.—I am, etc.,

J. B. TRAHERNE.

London S.W.2.

Obituary

R. H. THOMSON, *M.C.*, L.R.C.P.&S.Ed.

By the death of Dr. Robert H. Thomson on August 12 at the age of 73, West Lothian has lost one of its oldest and well-loved family doctors. He had practised at Uphall for nearly half a century.

Robert Howie Thomson, who was born on May 20, 1888, was a native of Fife, his father being manager of Cowie Pit. From Stirling High School he went on to study dentistry and medicine at the Royal College of Surgeons of Edinburgh. Qualifying in dentistry in 1911, he took the triple conjoint qualification two years later. During the first world war he served as a captain in the R.A.M.C. and was awarded the Military Cross. On demobilization he set up in practice in Uphall, West Lothian, and he remained there until his retirement in 1958.

A keen member of the B.M.A., he was honorary secretary of the West Lothian Division for a time during the second world war and was chairman of the Division on two occasions, in 1943–4 and again in 1951–3. He was also president of the Edinburgh and South-east Scotland Branch in 1955–6. An enthusiastic golfer, he was always happy in the company of his friends. He enjoyed all social functions and was a keen member of the East of Scotland Overseas Medical Club. He is survived by his widow, a son, and a daughter.

H. MINNIE LEVICK, M.B.E., M.D., B.Sc.

Dr. H. Minnie Levick (née Castledine) died at her home in Middlesbrough on August 15 at the age of 90.

Harriett Minnie Castledine was born on August 8, 1871. From Newnham College, Cambridge, where she obtained first-class honours in the Natural Sciences Tripos, she went on to the London School of Medicine for Women (Royal Free Hospital) and graduated B.Sc. of London University in 1895 and M.B. in 1898. She proceeded M.D. in 1901. She married Mr. Harry Driffield Levick, a consulting surgeon in Middlesbrough, in 1899. Together they introduced aseptic surgery to Middlesbrough, abolishing "laudable pus," and together they performed the first appendicectomy in the town. For many years she ran a successful nursing-home for her husband, who died in 1958 at the age of 91.

J. E. H. writes: During the second half of their working life Harry and Minnie Levick both gave themselves up to civic work. "Dr. Minnie" was a town councillor for six years and acted in that capacity during the town's centenary year, when "H. D." was mayor. She was formerly medical officer and part founder of the first voluntary child-welfare centre (1913 to 1918). An ardent supporter of the Girl Guides, she was a district and divisional commissioner and later president of the local Girl Guides Association. Dr. Levick served as chairman of the Municipal Hospital Committee, as president of the Middlesbrough branch of the National Council of Women, and chairman of committee and honorary medical officer of the first voluntary nursing school. A vice-president of the Middlesbrough Settlement, she had been a medical officer of the Board of Education under the superannuation scheme. She was chairman of the Cleveland Division of the B.M.A. in 1927–8 and was awarded the M.B.E. for her work as county organizer of the Women's Voluntary Service in 1944.

Dr. Minnie was indeed a remarkable person. Her clinical and administrative ability were beyond doubt, but it was to her guiding principle—truth—that one stood in awe. No matter what the occasion or the business, only the absolute truth as she saw it from a scientific point of view would do. Such unrelenting discipline gave her an appearance of

hardness which was so very much more apparent than real. All admired her courage and determination ; the fortunately more intimate enjoyed the same degree of loyalty and friendship.

O. R. BELCHER, L.R.C.P.&S.

Dr. O. R. Belcher, who practised for many years in the Anfield and Everton areas of Liverpool, died in London on August 1. He was 78 years of age.

Ormonde Rashleigh Belcher was born in Cork in 1883, and spent his childhood there. His family then moved to Glasgow while his father was serving as a ship surgeon on the transatlantic route. Later his father went into general practice in Liverpool, where Ormonde Rashleigh Belcher was to spend the remainder of his active life. He studied medicine at Liverpool University and qualified in 1908, thus continuing a family tradition which had lasted many generations.

After qualifying he held house appointments at the Northern Hospital in Liverpool, being house-surgeon to Mr. Monsarrat. He had a leaning towards ophthalmic surgery, but since his father had died before he qualified he went into general practice in the Anfield and Everton areas of the city and worked as a clinical assistant at St. Paul's Eye and Ear Hospital.

During the first world war he was a captain in the R.A.M.C., serving as an ophthalmic specialist in Taranto, Italy. On his return to civilian life he continued to practise in Anfield until he retired ten years ago. He held the appointment of medical officer to the Post Office and took an active part in medical affairs, being chairman of the local panel committee for some years, of the local medical war committee, and of the Liverpool Division of the B.M.A. from 1944 to 1946. His colleagues respected his exceptional ability, for he was quite fearless in his approach to any problem and invariably able to make a keen assessment of it. After giving up his general practice he continued with the work which he had done throughout the second world war on local medical boards, of one of which he was chairman for many years. Three years ago he gave up all his work and lived until very recently in Mossley Hill.

Dr. Belcher leaves a son, Mr. Jack Belcher, who is a surgeon in London, a daughter, and three grandchildren. His wife died 18 months ago.

J. G. DALGLEISH, M.B., Ch.B.

Dr. J. G. Dalgleish, who was in general practice in Sunderland for over 30 years, died in the Sunderland Royal Infirmary on June 2, aged 61 years.

John Gibb Dalgleish, the son of a schoolmaster, was born in Clydebank on January 28, 1900, and was educated at the Clydebank High School. Towards the end of the first world war he served in the Argyll and Sutherland Highlanders. He then studied medicine at Glasgow University and graduated M.B., Ch.B. in 1925. After holding resident posts in Glasgow he acted for a time as assistant in General practice at Ferryhill, Co. Durham, ultimately settling in Sunderland in 1927, joining the late Dr. John Anderson. After a few years he commenced on his own and built up a large practice, being later joined by Dr. A. Anderson and Dr. W. Stuart as partners. He served on the local panel committee and on the executive council.

Dr. A. A. McINTOSH NICOL writes: The sudden passing of John Dalgleish has left a gap in the medical life of Sunderland which will be most difficult to fill. He was the type of family doctor who was loved and respected by his patients and one who knew the majority of them by their Christian names. It was indeed a pleasure to be called in consultation by Dr. Dalgleish and to note that happy relationship which existed in his practice. He possessed a delightful personality, was always cheerful, and had that "couthiness" which one so often associates with a Lowland Scot. To those of us who had the honour of being his friends, Jack was a sterling character and a man who hated ostentation and outward show. He did not suffer fools gladly and never hesitated to state his opinions with candour. He loved his native Scotland and was full of its history and folklore, and was indeed an adept with his fund of Scottish humour. In his early days he was keen golfer and later a most enthusiastic fisherman.

To his wife, daughter, and son we extend our deep sympathy.

D. W. SMYTH, M.B., B.Ch., D.Obst.R.C.O.G.

Dr. David Smyth died at his home in Hereford on June 18 at the age of 36 years.

David William Smyth was born in Belfast and educated at Campbell College. He graduated M.B., B.Ch. at Queen's University, Belfast, in 1948, and after a year as house-surgeon at Ards District Hospital he served as ship surgeon in the Merchant Navy. He went to Hereford in 1950 as obstetrical house officer at the County Hospital and obtained the D.Obst.R.C.O.G. in the following year. He became a partner in a practice in Hereford in 1952.

Ready willingness, loyalty, and a delightful sense of humour made David Smyth a perfect colleague, and among his patients he made many real friends who valued his very human understanding of their problems. The happiness in his family life helped him to face illness with tremendous courage, and our deep sympathy goes out to his wife and two young sons.—G. N. W.

VERA FELLOWES, M.B., Ch.B.

Dr. Vera Fellowes, formerly assistant administrative medical officer of health for diphtheria immunization in Birmingham, died on July 19, in her 63rd year.

A colleague writes: The untimely death of Vera Fellowes so soon after her retirement has created a sense of loss not only among her former colleagues but among her public who frequented her diphtheria immunization clinics during the 30 years in which she was engaged so intensively in that work. Chosen by Dr. Matthew Burn to launch his scheme in the 1920s in schools and welfare centres in Birmingham, she readily lent her boundless enthusiasm to pioneer the work in Birmingham at a time when, apart from Edinburgh and Aberdeen, few local authorities seemed interested and no blessing had so far come from Ministry level. She was more fortunate than many in being able to see concrete results for her efforts. Never one to seek the limelight, she plodded along quietly building up the city's immunity to diphtheria with a complete disregard for normal working hours, and finding time as well to become and remain greatly beloved at a welfare centre in one of the poorest parts of the city. By her colleagues, however, she will be remembered mainly for her team spirit and for the skill and determination which she showed in investigation of the source of outbreaks of infection. "When in doubt, put Fellowes on to it," became almost routine policy. She will be greatly missed.

T. J. K. BROWNLEES, M.R.C.S., L.R.C.P., D.P.M.

Dr. T. J. K. Brownlees, who was senior hospital medical officer at Exminster Hospital, near Exeter, died on July 23 at the age of 53.

Thomas John Kilpatrick Brownlees was born in London on July 13, 1908, the son of the late Dr. J. K. Brownlees, who practised in North London. He studied medicine at St. Bartholomew's Hospital, qualifying in 1933. After resident appointments at the North Staffordshire Royal Infirmary and the Royal United Hospital, Bath, he joined

the staff of Exminster Hospital in 1934 and remained there for the rest of his professional life, except for service as a major in the R.A.M.C. during the second world war. He took the D.P.M. in 1937.

Dr. M. SIM writes: The news of Tom Brownlees's death will bring sadness to all his colleagues and particularly to those who were privileged to know him at the Forty-first Psychiatric Hospital in the Middle East. He was one of "Nature's gentlemen" who by his quiet manner and conscientious devotion to his patients set an example of dedicated doctoring which few could match. He was a first-class psychiatrist, and it was not surprising that he was the specialist chosen from the Forty-first to undergo battle experience at Alamein. Unfortunately a severe attack of rheumatic carditis resulted in his early evacuation, and this disability has just contributed to his death. He refused to be sent home and continued to serve with the Forty-first, and on his release from the Forces returned to Exminster Hospital, where he remained. He was reticent and aloof and did not attract a wide circle of friends, but all who knew him were enriched by his unselfish, humane approach to medicine, and impressed by his indifference to the status symbols of success. His ambitions were much higher, and he achieved them.

J. T. SMALLEY, M.R.C.S., L.R.C.P.

Dr. J. T. Smalley, who served in the Colonial Medical Service first in Fiji and then in Hong Kong, died in Cambridge on August 17.

James Thornton Smalley, who was born in 1882, was the son of Major-General F. Smalley, of the Indian Army. Qualifying at Guy's Hospital in 1907, he held the posts of out-patient officer and house-surgeon at Guy's and then went out to Fiji as resident medical officer at the Colonial Hospital, Suva. Later he became medical officer of health and port medical officer at Seonka. He moved to Hong Kong in 1913, and one of his first posts there was medical officer in charge of Kowloon and the New Territories. In 1931 he was promoted senior medical officer and later became deputy director of medical services. He retired to Cambridge some years ago and was chairman of the Ministry of Pensions medical board there and consultant in tropical medicine to the East Anglian regional hospital board.

Sir PHILIP MANSON-BAHR writes: I would like to pay a brief tribute to my very old friend, of over 50 years' standing, James Smalley. He was there to greet me when I at last arrived in Fiji on January 12, 1910. He was then fresh from Guy's and married to an ex-surgical sister of the same hospital. He was bubbling over with surgical enthusiasm and was very soon to prove his quite outstanding boldness and skill in tackling many of the strange and unfamiliar surgical conditions with which he found himself surrounded. Of these weird and wonderful things, the most part were of filarial origin. It proved to be the paradise of the Pacific form of *Filaria bancrofti*, as this parasite was properly known in those days. There were elephantoid tumours of the arms, legs, and breasts, hydroceles, and enormously enlarged lymphatic glands. There were also some poor wretches with high fever and ankylosis of the hip hitherto diagnosed as tuberculous disease. These he soon proved to be of filarial origin, secondarily infected with streptococci, so that they could be successfully treated by drainage.

Had it not been for James Smalley and his surgical adventures I would have been quite unable to prosecute my studies on the pathology of filariasis. I can never forget his efficiency and kindness to my wife and myself when he brought my eldest daughter into the world, now over fifty years ago.

Truly Smalley was an outstanding surgeon who has left a great reputation behind him in the Colonial Service.

J. J. KEMPTON, M.B.E., M.D., F.R.C.P.

The obituary of Dr. J. J. Kempton was published in the *Journal* of August 5 (p. 388).

A. J. F. writes: Dr. Jack Kempton was a fine paediatrician and a man for whom it was an honour to work. He was always courteous to parents and to the nurses and doctors on his wards, and such was his concern for his young patients that he drew out of those around him the best service they could give. It was a delight to see a refractory child with its harassed mother enter his consulting-room, when his calm and kindly manner would quickly instil confidence into both. He had an immense store of fun, and never lost a child-like sense of wonder at the skills of his professional colleagues, while at the same time keeping abreast of the recent advances in his own specialty. He delighted to demonstrate his own considerable skill to a new house-physician trying to master the technique of the scalp-vein apparatus which bears his name. The only time I saw him show annoyance was when he was faced with some piece of obstructiveness by petty officialdom, and then he would himself set about solving the problem by a direct approach between heads of departments. He has left us a fine example of service to the children he loved.

W. R. M. writes: I shall always remember Dr. Kempton's ward rounds, which were attended not only by residents at the Royal Berkshire Hospital but also by many general practitioners. Students from St. Mary's used to spend a week at a time in his department, living in at the hospital. He was a fine teacher, interesting and approachable.

Dr. R. A. RATCLIFF writes: Many people, both professional and lay, would be very glad to see tribute paid to Dr. Jack Kempton's outstanding and individual service to general paediatrics, as well as to the special departments mentioned in other notices. He combined a large knowledge of all branches of paediatrics with assiduous study and an open and receptive mind, leading to his increasing wisdom, of irreplaceable value to all patients and doctors needing his help. To this was added a capacity for securing the co-operation of senior colleagues, hard work willingly done from his juniors, and loyal respect from the administrators. He was equally helpful to all who work under the three separate parts of the National Health Service Act. Beyond this, his paediatric teaching of local doctors and of students of various kinds was well informed and gave a balanced account of all recent developments, leading to the great popularity of his teaching rounds. The paediatric department of the Royal Berkshire Hospital owes so much to his organization that in future years the effect of his planning, from the prezygotic stage through the embryonic to the well-developed department, will be manifest to many who remember him with gratitude.

J. PRESTON MAXWELL, M.D., F.R.C.S. F.R.C.O.G.

The obituary of Professor J. Preston Maxwell was published in the *Journal* of August 12 (p. 457).

Dr. NICHOLSON J. EASTMAN, professor emeritus of obstetrics, Johns Hopkins University School of Medicine, Baltimore, writes: It falls to few men to revolutionize a branch of medicine to the extent that J. Preston Maxwell revolutionized the practice of obstetrics and gynaecology in China during his four decades of service there. He found it a miserable trade in the hands of completely ignorant and illiterate midwives, with only a handful of Occidental specialists scattered in a few treaty ports. He left it a thriving young specialty whose personnel included hundreds of competent Chinese obstetricians and gynaecologists and thousands of superbly trained Chinese midwives. This he was instrumental in accomplishing in two ways: first, through the training he gave to a succession of young men and women on his staff; and, second, through the medium

of his great protégé, Dr. Marion Yang, who between 1927 and 1935 organized more than 40 midwife schools distributed throughout all the provinces of China.

In the field of research his monograph on osteomalacia first documented the true nature of the disease and is a classic. He was a man of extraordinary vigour to the last, both mentally and physically. Indeed, after retirement from his post in Peking he served and was successively "retired" from a number of arduous clinical posts in England. Moreover, if he could have had his own way about it he would have functioned in the second world war (at the age of 70) as a first-line ambulance surgeon; and he would doubtless have done an excellent job.

As a young man, and especially as an American, it was a high privilege to serve for some six years under this great British obstetrician and gynaecologist. The mothers of China will ever be his debtors, as will also those of us who are proud to count ourselves among his pupils.

Sir WALTER FERGUSSON HANNAY
M.R.C.S., L.R.C.P.

The obituary of Sir Walter Fergusson Hannay was published in the *Journal* of August 26 (p. 589).

MR. A. DICKSON WRIGHT writes: With the death of Sir Walter Leisrinck Fergusson Hannay the profession has lost a colourful and invigorating personality. He affected an old-world appearance, took snuff with old-time grace and elegance, and thus readily caught the eye at medical meetings, at which he was a regular attender and a frequent speaker, and this led to his election as president of the Chelsea Clinical Society—always a signal honour, especially for a general practitioner. He wrote many letters to the lay press speaking forcefully against the National Health Service, although he was a friend and doctor to the Premier who saw it through the Houses of Parliament. Another topic upon which he dilated was the evil of noise (he was chairman of the Noise Abatement Society). The abominable fumes of diesel engines enraged him, and, sad to say, he died from the very disease they are said to produce.

With a flaming mop of red hair he entered Guy's in 1923 from Berkhamsted School and passed through in the minimum time, gaining many "A5s" on his way as he carried out his clinical posts under the memorable staff of Guy's in those years. After various house appointments he went into general practice in South Kensington, moving later to Harley Street, where, as an individualist, he liked to work alone and established a considerable practice including very many notable people. Busy as he was, he always found time to work, and work regularly, as voluntary clinical assistant at various hospitals.

A great event in his life was his marriage to Doris Leslie, the historical novelist, nearly 25 years ago. They made a wonderful partnership, and he gloried in her success and contributed to it not a little by his suggestions and his wide historical knowledge. It was a great joy to visit them in their noise-proof home in Hertfordshire and listen to the brilliant banter which constituted most of their conversation. His wife was a great comfort to him in the miserable illness which ended his days. Right through it all he never lost the merry twinkle of eye and attractive chuckle with which he always managed to greet one. His sense of humour was ever in evidence, always enjoyable, and never spiteful; it must have been a family feature, because his relative, Canon Hannay, wrote books under the name of George Birmingham, books that rank with those of Jerome K. Jerome, Stephen Leacock, and Mark Twain for humour that will last for all time.

Towards the end of his life both he and his wife embraced the Catholic faith, and indeed he made a trip to Lourdes, during which he had a heavy fall which broke his back. Many of his friends and patients (and the terms were often synonymous) gathered at the Requiem Mass at St. Dominic's Priory to say a last farewell to a dear character whose memory will live for a long time.

Vital Statistics

Cholera in Hong Kong

Up to August 28 there had been 84 cases of cholera in Hong Kong with 10 deaths: 30 patients were in hospital, and 307 contacts and 35 carriers were isolated. About 2,000,000 of Hong Kong's population of over 3,000,000 have now been vaccinated.

Infectious Diseases

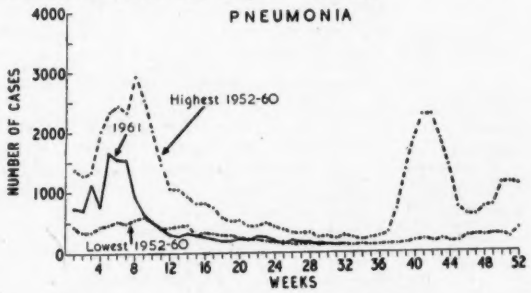
During the week ended Saturday, August 19, 19 paralytic and 6 non-paralytic cases of poliomyelitis were notified in England and Wales: 10 of these cases occurred in Lancashire (2 in Southport and 2 in Tyldesley). There were four cases of paratyphoid fever in Glasgow.

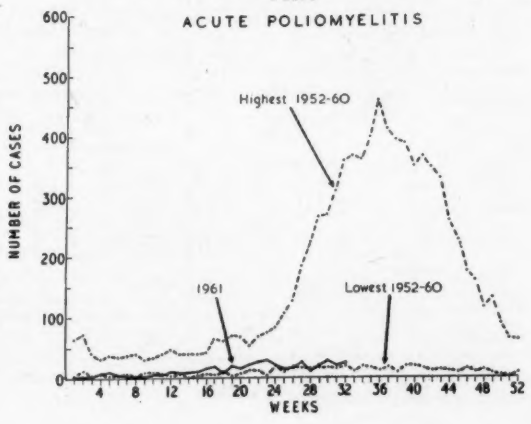
Road Casualties in June

Of the 525 people who were killed in road accidents during June, 169 were drivers or passengers in cars and other vehicles, 159 were pedestrians, 133 were motor-cyclists, scooter or moped riders, and 64 were pedal cyclists. In addition 7,374 people were seriously injured and 22,802 slightly injured. The total number of road deaths during the first six months of 1961 was 3,187, an increase of 6% compared with the same period last year. Casualties among car drivers and passengers continued to show a large percentage increase (16%) compared with the first six months of 1960. Motor traffic generally is estimated to have increased by 9% over the same period and car traffic in particular by 12%.

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1952–60 are shown thus ------, the figures for 1961 thus ———. Except for the curves showing notifications in 1961, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.





INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **August 12** (No. 32) and corresponding week 1960.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1961					1960				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	2	0	0	0		2	0	0	0	1
Dysentery ..	253	78	121	9	8	427	64	191	5	2
Encephalitis, acute	2	0		2		8	0	1	0	
Enteric fever:										
Typhoid ..	6	0	0	0		3	0	1	0	
Paratyphoid ..	3	0	3(B)	1		6	1	0	0	
Food-poisoning ..	118	13	26	0		230	27	19	1	
Infective enteritis or diarrhoea under 2 years ..				14	22				7	24
Measles*	6,277	120	22	84	71	2,544	133	48	6	18
Meningococcal infection	12	2	3	1		25	2	19	0	
Ophthalmia neonatorum	18	5	2	0		17	2	4	0	
Pneumonia† ..	118	12	78	1		130	9	101	0	
Poliomyelitis, acute:										
Paralytic ..	19	1	1	0	3	7	3	0	0	7
Non-paralytic ..	4	0	0			11	0	1		
Puerperal fever§ ..	181	34	10	0		181	27	7	0	1
Scarlet fever ..	210	10	15	3	6	252	14	29	10	8
Tuberculosis:										
Respiratory ..	298	26	37	9		366	36	74	12	
Non-respiratory	36	5	10	0		62	4	10	1	
Whooping-cough ..	296	18	47	11	17	1,384	120	117	13	39

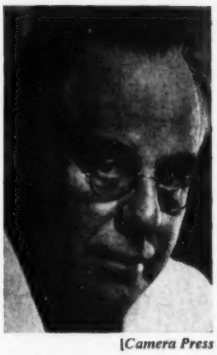
DEATHS	1961					1960				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	0	0	0	0	0	0	0	0	0	0
Dysentery ..	1	0		0		2	0		0	
Encephalitis, acute		1			0		0			0
Enteric fever ..	0	0	0	0		1	1	0	0	
Infective enteritis or diarrhoea under 2 years	2	0	0	0	1	7	1	0	0	0
Influenza	3	1	0	0	0	3	0	0	0	0
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		0	0				1	0		
Pneumonia ..	377	29	18	13	8	353	21	14	9	4
Poliomyelitis ..	1	0		0	0	1	0		0	0
Scarlet fever ..		0	0	0	0		0	0	0	0
Tuberculosis ..										
Respiratory ..	51	4	5	0	0	68	9	3	0	5
Non-respiratory				1	0		2	0	1	0
Whooping-cough ..	0	0	0	0	0	0	0	1	0	0
Deaths 0–1 year ..	276	20	25	4	12	277	22	20	6	11
Deaths (excluding stillbirths) ..	8,113	618	484	112	104	8,441	673	485	113	170
LIVE BIRTHS ..	14,537	1177	991	238	421	15,241	1254	1003	275	349
STILLBIRTHS ..	273	15	35			312	25	20		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

British Association Presidential Address

The British Association returned to Norwich for its 123rd annual meeting from August 30 to September 6. It had met there previously in 1868 and 1935. The Presidential Address, on "The Humanity of Man," was delivered by Sir WILFRID LE GROS CLARK, F.R.S. He believed that, just as many individuals take stock of their failures and achievements at the end of each year, we should now take stock of the species *Homo sapiens*, and ask ourselves whether the human species can avoid at least partial extinction by the misapplication of its own ingenuity. He then gave a review of how we came to be and how we are constituted in our physical and psychological adaptability to cope with the changing environment in which we find ourselves to-day. He believed that the emergence of the biological species *Homo sapiens* had been the resultant of selective pressures directly dependent on the invention and development of cultural organizations of increasing complexity. "It may be said, indeed, that if man (in the broadest sense) invented culture, it was culture which invented *Homo sapiens*." In spite of intervals of stagnation and regression there had been a broad historical trend towards the unification of mankind. This historical process had tended to slow up as populations become opposed to each other by conflicting economic and ideological interests.



[*Camera Press*

An essential prerequisite for any attempt at further unification was the ability to give full expression to the impulse for co-operation, and this could only be made possible by the free interchange of ideas among the populations of the world. Sir Wilfrid believed that in promoting such an ideal science had a vitally important part to play. He traced the development of international scientific associations from the middle of the last century, instancing the International Geophysical Year of 1957 to 1958 as one of the most outstanding examples of intimate collaboration between scientists of many nations for the benefit of mankind in general. The task of the British Association itself was to inculcate as widely as possible that spirit of freedom in scientific inquiry which gave full expression to the deep-rooted altruism which, as Sir Wilfrid said he had tried to emphasize, was an essential attribute of the humanity of man, and which he believed could do more than anything else to preserve harmony among all peoples of the world. But the dangers threatening the unity of mankind were formidable indeed. "And time," said Sir Wilfrid, "is getting very short."

Director, Bureau of Hygiene and Tropical Diseases

Dr. H. J. O'D. BURKE-GAFFNEY, assistant director of the Bureau of Hygiene and Tropical Diseases, has been appointed to succeed Dr. CHARLES WILCOCKS when the latter retires from the directorship of the bureau, which he has held since 1942, on November 30.

Dr. Burke-Gaffney qualified in medicine from Trinity College, Dublin, in 1924, proceeding M.D. in 1931. He gained the certificate of the London School of Hygiene and Tropical Medicine in 1925. While a member of the Colonial Medical Service he was awarded the North Persian Forces Memorial Medal in 1932 for a paper dealing with the classification of the coli-aerogenes group of bacteria. He has served as senior pathologist, Tanganyika, and as officer in charge of Civil Defence Casualty Services, Dar-es-Salaam. He was appointed to his present post in 1946. Dr. Burke-Gaffney is the author of *Outline of Clinical Pathology* (2nd ed., 1949), and was a contributor to

The Times Survey of British Colonies (1950), and *The Times British Colonies Review* (1953). He was appointed O.B.E. in 1942.

Mines and Quarries Report

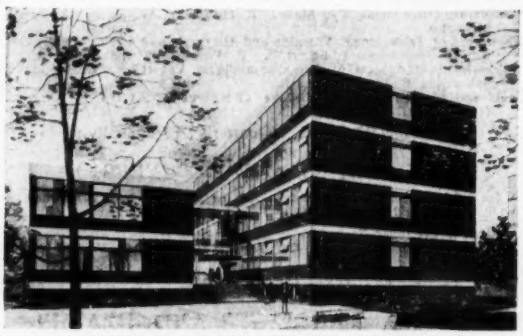
The *Report of H.M. Chief Inspector of Mines and Quarries for 1960* makes the comment that at least half of the serious accidents occurring every year could be avoided by compliance with the law or by the exercise of ordinary care. In 1960 317 men were killed and 1,573 seriously injured, compared with 348 killed and 1,676 seriously injured in 1959. Taking into account that fewer manshifts were worked in 1960, there has been no improvement in the rate for persons killed and a deterioration in that for persons injured. The number of fires in coal mines is increasing: 76 in 1960 compared with 71 in 1959. Figures for new cases of diseases other than pneumoconiosis at coal mines in 1960 are as follows (figures for 1952 in brackets): dermatitis, 3,201 (3,863); beat hand, 167 (454); beat knee, 7,122 (9,118); beat elbow, 728 (1,260); inflammation of wrist, 526 (693; nystagmus, 58 (191). In quarries 38 persons were killed and 93 seriously injured as against 30 and 94 the year before. (H.M.S.O., price 4s.)

Hospital Building Notes

The latest in the Ministry of Health's series of Hospital Building Notes, No. 13, *Central Sterile Supply Department*, gives guidance on the design and and recommendations as to cost of a central sterile supply department at a district general hospital or teaching hospital. The department described in the note will serve 800 beds or upwards with related diagnostic and treatment facilities for out-patients and casualties. Central sterile supply departments are still in an early stage of development in the United Kingdom and there may well be acceptable proposals which differ considerably from those proposed in this note. The cost of such proposals may have to be individually assessed. (H.M.S.O., price 1s. 6d.)

New Headquarters for Birmingham Regional Hospital Board

A new headquarters office block is being built in Hagley Road for the Birmingham Regional Hospital Board. In addition to administrative staff, the building will contain



Birmingham Regional Board's new offices.

architectural and engineering departments and an electronic computer centre to provide accounting services for all hospitals within the region.

Royal Society of Health's Subject Groups

A number of specialist subject groups are to be formed by the Royal Society of Health. A start is to be made with groups covering building and estates; dental health; food and nutrition; medical auxiliaries; ophthalmic subjects; pharmaceutical subjects; public health nursing; and social and welfare subjects. Meetings will be convened for the presentation of papers and their subsequent discussion at a more specialized level than is possible at existing meetings. The holding of the latter will be unaffected by the new arrangements. A special bulletin dealing with group news as well as with papers read at group meetings will be circulated to members with each issue of the Society's journal.

Australia and Dentists

▶ The Federal Council of the Australian Dental Association has called for the establishment of an Australian College of Dental Surgery to conduct postgraduate courses and examinations, and to confer fellowships. The A.D.A. had formed a committee to work for the establishment of the college. The council has also renewed demands for a Government-sponsored dental benefits scheme. The council will make a survey of dentistry throughout Australia covering the distribution of dentists, the economics of dental practice, and the need and demand for dental treatment.

▶ Action has been urged by the New South Wales Minister of Health, Mr. W. SHEAHAN, against Australian dentists who leave their country to practise in Great Britain. He said Australia could not compete with overseas offers of homes and practices, and added that in recent years 500 Australian dentists had migrated to the United Kingdom, 300 of whom had been trained in New South Wales. (*The Times*, August 23.)

Winding Up of Association for the Paralysed

The National Association for the Paralysed, founded in 1948, is winding up its affairs as a separate body to avoid duplication of work with State and voluntary bodies serving the disabled. The information, publication, and advisory services of the National Association's work will be carried on from September 14 by the Central Council for the Care of Cripples, 34 Eccleston Square, London S.W.1.

Homes of St. Giles for British Lepers

The Homes of St. Giles for British Lepers were founded in 1914 on an estate of 27 acres with a small farmhouse in a secluded part of Essex. Since 1936 the patients have been looked after by the Community of the Sacred Passion, an Anglican order devoted to the care of patients with leprosy in Tanganyika to whose Sisters the Homes serve as an English rest house. The Homes, which can accommodate 18 patients, are maintained by voluntary subscriptions. An appeal is being launched for £20,000 to provide additional accommodation for Sisters who are unable to return to Africa because of age or ill-health. The Secretary is Mr. G. LE BLOUNT KIDD, 60 Lincoln's Inn Fields, London W.C.2.

Register of Operating Theatre Technicians

The 1961 (fifth edition) of the *Register of Medical Auxiliary Operating Theatre Technicians* has now been published by the Board of Registration of Medical Auxiliaries. Copies of the *Register* will be sent free to members of the medical profession, hospitals, and official bodies on application to the Registrar, Board of Registration of Medical Auxiliaries, B.M.A. House, Tavistock Square, London W.C.1.

"Midland Medical Review"

The *Birmingham Medical Review* has changed its title to *Midland Medical Review*. Its new editor, Mr. G. T. WATTS, succeeds Dr. H. W. FEATHERSTONE. The *Review* is published quarterly by the Birmingham Medical Institute (36 Harborne Road, Edgbaston, Birmingham 15) and costs £1 a year, or 5s. a copy.

"Vision Research"

Vision Research, a new journal published at the moment at irregular intervals, will be concerned with any problem relevant to visual science; it will accept direct experimental studies, reviews, and theoretical articles, but not clinical and *ad hoc* papers. Papers may be in either English, French, or German, with a three-language abstract. Professor A. SORSBY is on the board of editors, and papers may be addressed to him at the Department of Ophthalmological Research, Royal College of Surgeons of England, Lincoln's Inn Fields, London W.C.2. The publishers are Pergamon Press, Ltd., Headington Hill Hall, Oxford, and the annual subscription for individuals is £3 10s. ($10), for organizations £10 ($30).

"Family Doctor"

The September issue of *Family Doctor* is now on sale, at 1s. 6d., and includes articles on going to school, by Professor R. S. ILLINGWORTH; on the effect of sweets on teeth, by Dr. E. J. TRIMMER; on menstruation, by Miss JOSEPHINE BARNES; on sex education, by Dr. J. A. C. BROWN; and on diets for teenagers, by Dr. ANN MULLINS.

Grants, Gifts, and Bequests

Dr. D. SNELLGROVE, a retired medical practitioner and chairman of Luton Old People's Welfare Committee, has been given a grant of £300 by the National Corporation for the Care of Old People to investigate the social and financial conditions of elderly people in Luton whose infirmity keeps them indoors. The N.C.C.O.P. will publish his results.

In Brief

The Hebrew University Hadassah Medical School in Jerusalem is to provide medical training for 20 Afro-Asian students in November. The cost will be borne by the World Health Organization and the Israeli Government. (*New York Times*, August 23.)

People in the News

Sir STANFORD CADE has been appointed a member of the advisory committee on the administration of the Cruelty to Animals Act, 1876, in place of Sir GEOFFREY KEYNES, who has resigned.

COMING EVENTS

7th International Congress for Internal Medicine.—Munich, September 5–8, 1962. Main topics: "Immunity Processes in the Pathogenesis of Internal Diseases," "Shock and Collapse in Internal Medicine," "Environment and Disease." Details from Congress secretariat, 62 Schwalbacherstrasse, Wiesbaden, Germany.

Rudolf Steiner Schools and Homes for Handicapped and Maladjusted Children.—Exhibition September 8 and 9, Rudolf Steiner Hall, 35 Park Road, London N.W.1.

"Mental Stress."—Demonstration by Professor H. J. EYSENCK and colleagues using large-screen colour television. Sponsored by C.I.B.A. Laboratories Ltd., September 13, 8.30 p.m.; September 14, 6 p.m. French Institute, Queensbury Place, London, S.W.7. Admission by ticket only from C.I.B.A. at Horsham, Sussex.

Clean Air and Clean Food Exhibition.—Borough of Ealing, Public Health Department, Town Hall, Ealing, London W.5, September 27–October 4. Parties wishing to be shown round separately should write to Mr. A. BAMPING at that address (EALing 3030).

Institute of Psychiatry.—Symposium for consultant psychiatrists, "The Future of the Mental Hospital," October 5, 6. Details from and applications (fee £3 3s.) to the Dean, Institute of Psychiatry, Maudsley Hospital, Denmark Hill, London S.E.5, before September 15.

2nd Asiatic Congress of Obstetrics and Gynaecology.—Calcutta, January 23–25, 1962. Subjects for discussion: "Malignant Tumours of the Female Genitalia," "Toxaemia of Pregnancy," "Maternal and Perinatal Mortality." Details from Honorary Secretaries of Congress, 4 Chowringhee Terrace, Calcutta 20, India.

NEW ISSUES OF SPECIALIST JOURNALS

The journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London W.C.1.

BRITISH JOURNAL OF PHARMACOLOGY AND CHEMOTHERAPY

Proceedings of the British Pharmacological Society, Edinburgh, July 12 to 15.

Some Observations on Pecking in Pigeons. V. R. Deshpande, M. L. Sharma, P. R. Kherdikar, and R. S. Grewal.

Suppression of Ouabain-induced Atrial Arrhythmias by Carotid Sinus Stimulation. A. Schott.

Comparison of the Functional Effects of Dyflos, Tri-*o*-cresyl Phosphate and Tri-*p*-ethylphenyl Phosphate in Chickens. J. B. Cavanagh, D. K. Davies, P. Holland, and M. Lancaster.

A Multiple Toe-pinch Method for Testing Analgesic Drugs. H. O. J. Collier, B. T. Warner, and Rita Skerry.

The Effect of Atropine, Propantheline and Poldine on the Vagally Stimulated Gastric Motility and the Histamine-stimulated Acid Gastric Secretion in the Rat. P. N. Aarsen and J. Van Noordwijk.

Studies on the Slow Contraction of Smooth Muscle Produced by Human Plasma. Y. Gabr.

Effects of Drugs on Partially and Completely Denervated Skeletal Muscle of the Frog. G. B. Frank.

Pharmacology of Methicillin. P. Acred, D. M. Brown, D. H. Turner, and D. Wright.

Action of Bretylium on the Isolated Guinea-pig Ileum. H. W. Kosterlitz and G. M. Lees.

Effect of Reserpine on the 5-Hydroxytryptamine and Adenosine-triphosphate of the Dog Intestinal Mucosa. W. H. Prusoff.

The Distribution of Some Quaternary Ammonium Salts in the Peripheral Nervous System of Cats in Relation to the Adrenergic Blocking Action of Bretylium. A. L. A. Boura, W. G Duncombe, and A. McCoubrey.

Rate of Antagonism of Tubocurarine by Potasium Ions. R. Creese, D. B. Taylor, and B Tilton.

Analgesic-antipyretic Drugs as Inhibitors of Kallikrein. B. J. Northover and G. Subramanian.

The Neuromuscular Blocking Action of γ-oxaloiaudonium Bromide. R. T. Brittain, H O. J. Collier, and P. F. D'Arcy.

Peripheral Actions of Hexamethonium in Relation to the Decreasing Effects of Repeated Doses on the Blood-pressure of Anaesthetized Rats. J. G. Blackman and R. Laverty.

A Note on the Distribution of [^{14}C]-Histamine Added to Blood. S.-E. Lindell and K Viske.

Sensitivity of the Hyperthyroid and Hypothyroid Mouse to Histamine and 5-Hydroxytryptamine. P. S. J. Spencer and G. B. West.

Assay of Substance P on the Fowl Rectal Caecum. J. Cleugh, J. H. Gaddum, P. Holton, and E. Leach.

Volume 17, No. 1. (Bi-monthly; £6 6s. annually.)

BRITISH JOURNAL OF VENEREAL DISEASES

Special issue devoted to symposium on "Gonorrhoea and Non-gonococcal Genito-urinary Infections" held in Cracow, September, 1960.

The Problem of Gonorrhoea with Special Reference to England and Wales. A. J. King and C. S. Nicol.

Epidemiology and Control of Gonorrhoea in Poland. T. Z. Capinski and J. Bachurzewski.

Gonorrhoea and Non-Gonococcal Infections. P. Durel.

Gonorrhoea in Denmark. A. Perdrup.

Gonorrhoea and Its Control in Finland. A. S. Härö.

Present Situation of Gonorrhoea in Italy. G. Tassi.

Campaign Against Gonorrhoea in Hungary. I. Károlyi, F. Földvari, and L. Kovács.

Epidemiological Aspects of Gonorrhoea in Oporto, Portugal. M. Cardia and A. da Fonseca.

Epidemiology of Gonorrhoea in Bulgaria. P. Botzov.

Urethro-genital Gonococcal Suppurations Observed During the Past Three Years in the Charles Nicolle Hospital, Tunis. A. Khalfat.

Gonorrhoea in Teenagers. I. S. Nielsen.

Difficulties of Diagnosis and Treatment of Gonorrhoea in Young Girls. B. Michalowski.

Sensitivity of *N. Gonorrhoeae* to Antibiotics. A. Reyn.

A Comparison of Sensitivity to Penicillin of *N. Gonorrhoeae*, 1960 and 1958. E. H. Letchner and C. S. Nicol.

Treatment of Gonorrhoea with Phenethicillin (Broxil). F. J. G. Jefferiss and N. Rosedale.

Clinical and Microbiological Observations on Non-Gonococcal Infections of the Male and Female Genito-Urinary Tract. K. Lejman and J. Bogdaszewska-Czabanowska.

Non-Gonococcal Vaginitis. M Cardia.

Studies on Trichomoniasis in Males. B. Hoffmann, W. Kilczewski, and E. Malyszko.

Treatment of Trichomonal Vaginitis and Urethritis and Their Complications with Metronidazole ("Flagyl"). P. Popchristov and V. Berov.

Epidemiological Aspects of Lymphogranuloma Venereum. C. Plácido de Sousa and F. Norton Brandão.

Incidence of Pleuro-Pneumonia-Like Organisms (P.P.L.O.) in Man. J. Horoszewicz.

Volume 37, No. 2. (Quarterly; £3 annually.)

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Friday, September 8

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. J. R. Bignall: clinical demonstration.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Nathanson.—On August 15, 1961, to Margaret (formerly Milman), wife of Dr. N E. Nathanson, a son.

O'Donoghue.—On August 11, 1961, at the Hospital of St. John and St. Elizabeth, London N.W., to Ruth (formerly Bachin, of Basle, Switzerland) and Dennis Michael, a son—Michael Francis.

DEATHS

Dalgleish.—On June 2, 1961, at Sunderland Royal Infirmary, John Gibb Dalgleish, M.B., Ch.B., aged 61.

Lennon.—On July 19, 1961, in a nursing home, Thomas Emmett Lennon, M.D., M.R.C.O.G., of West Kirby, Cheshire, aged 53.

Logan.—On July 18, 1961, in New Zealand, Dorothy Cochrane Logan, M.D., of 137 Harley Street, London W.

Lowry.—On July 24, 1961, at Swarthmore, Gerrards Cross, Bucks, Eleanor Lowry, M.B., B.S., D.P.H., aged 84.

Marks.—On July 27, 1961, at his home, 11 Draycombe Drive, Morecambe, Lancs, Gerald Johnson Marks, M.B., Ch.B., aged 59.

Smith.—On July 28, 1961, at Nelson, New Zealand, Alexander Campbell Smith, M.D., aged 92.

Turner.—On July 30, 1961, at "Moorlands," Telegraph Road, Heswall, Wirral, Cheshire, Robert Lindsay Turner, O.B.E., T.D., M.B., Ch.B., F.R.C.S.Ed.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Lobidan and Smoking

Q.—*A preparation of buffered lobeline ("lobidan") has been advertised as a smoking cure. Is it efficacious?*

A.—It has been suggested that the use of lobeline may help the nicotine addict who genuinely wishes to stop smoking to overcome his craving. Recently a proprietary preparation (lobidan) containing lobeline and a mixture of rapid- and slow-acting gastric antacids has become available in Great Britain. A short-term clinical trial[1] in the U.S.A. suggested that this preparation was of immediate help in assisting people who were really anxious to stop smoking. At the end of one month, however, the proportion of those who had used the lobeline preparation and were still not smoking was only 53%, and it is doubtful if this result is any better than might have been achieved by firm encouragement.

The side-effects are similar to those of nicotine, and will be familiar to anyone who remembers his first experiences with smoking. Addiction is said not to occur, but in view of the similarity to nicotine it seems possible that anyone who took a smoking deterrent containing lobeline for more than a short period might transfer his addiction from nicotine to lobeline.

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[1] Rapp, G. S., and Olen, A. A., *Amer. J. med. Sci.*, 1955, **230**, 9.

Oestrogens for a Transvestist

Q.—*I have a male transvestist patient aged 25 who has had a "cosmetic" operation (castration, amputation of penis, and the construction of a "vagina"). Oestrogens are required to maintain breast development. Could some dosage schedule be suggested? What are the dangers of this therapy? Would any possible dangers be influenced by using intermittent dosage instead of continuous? Oral therapy would be preferred to implants.*

A.—The most satisfactory way of inducing breast development in the patient described would be to give an implant of 100 mg. oestradiol. No further treatment would then be needed for perhaps two years—and none might be necessary afterwards. However, if oral therapy is preferred then stilboestrol 2 mg. daily would be the cheapest. A larger dose could be given—say 5 mg. daily—but might produce too much nausea to be tolerated.

The main drawback to oral therapy, apart from the need to continue it for a long time, is the likelihood of gastro-intestinal side-effects (mainly nausea, with or without vomiting). Theoretically—but only theoretically—there is a risk of carcinogenesis, and, again theoretically, this might be lessened by interrupted treatment (omitting it for 7–10 days after each month's treatment).

Risks in Rhesus Incompatibility

Q.—*What are the chances of an immunized rhesus-negative mother having a live baby? What progress has been made in the control of the formation of antibodies which have caused this woman to have so far one stillborn child, one abortion at three months, and one baby at term, which died after an exchange blood transfusion, suffering from severe kernicterus? This patient's first child was well, and is alive.*

A.—The chances of an immunized rhesus-negative mother, such as the one described, having a live baby depend upon several factors, the most important being the rhesus genotype of her husband. If he is heterozygous rhesus-positive, then there is a 50% chance that any baby will be rhesus-negative and therefore unaffected by haemolytic disease. If, however, he is homozygous rhesus-positive, then it is to be expected that all subsequent children of this mating will be affected, and the prospects of their survival depend on (*a*) the degree to which previous babies have been affected, and (*b*) the management of the subsequent pregnancies. In this particular case rhesus sensitization was almost certainly *not* the cause of the abortion, and, from the information given, it is not clear whether it was responsible for the stillbirth. Only the death of the last child can for certain be credited to haemolytic disease.

Townsend *et al.*[1] recently found that when a mother has lost a baby from rhesus incompatibility the perinatal mortality amongst her subsequent rhesus-positive children is 54%. The prospects are almost certainly better than this when the previous baby was still alive at term, as in the case in question. When a baby suffering from haemolytic disease is born alive and non-hydropic at term, it is usually possible to save its life and to prevent kernicterus by the use of *repeated* exchange transfusions to maintain the serum bilirubin below the critical level. To limit the effect of antibodies, premature induction of labour might also be considered in the management of a future pregnancy in this case. Various methods of predicting the ideal time for induction (antibody titres or avidity, liquor bilirubin estimations, etc.) are used, but there is no agreement on standards or on the best methods. In some centres the date is decided merely on the previous history.

With regard to the matter of controlling antibody formation, there is no satisfactory means of influencing this once sensitization has occurred. Attempts are being made to devise a method to prevent sensitization by detecting and destroying rhesus-positive foetal cells as soon as they cross the placental barrier into the maternal circulation.[2] This approach, however, is only in the early stages of development, and it is too soon to say whether it will prove effective. It is not applicable to the sort of case posed in the question, in which the mother is already sensitized.

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[1] Townsend, S. L., Mackay, E. V., Shelton, J. G., Krieger, Vera I., and Campbell, Kate I., *J. Obstet. Gynaec. Brit. Cwlth*, 1961, **68**, 382.
[2] Finn, R., Clarke, C. A., Donohoe, W. T. A., McConnell, R. B., Sheppard, P. M., Lehane, D., and Kulke, W., *Brit. med. J.*, 1961, **1**, 1486.

Prophylactic Antitetanus Serum

Q.—*Four weeks ago I had a serum reaction following an injection of prophylactic antitetanus serum. Would it be safe for me to have a third polio vaccine injection which is due now?*

A.—Polio vaccine does not contain any serum, and you should have the third injection as soon as convenient. There are practically no reactions to this prophylactic, and certainly no more in persons who have at any time shown a reaction to horse serum.

Porphyria

Q.—*Can anything be done to prevent the recurrent attacks of acute abdominal pain in a boy aged 15 suffering from porphyria? What is the prognosis?*

A.—Recurrent attacks of symptoms due to porphyria can be stopped only if the immediate cause can be determined, which very often is the case. The most important matter to consider is drug therapy, especially any drug chemically related to, or containing in part, barbiturates. These drugs are commonly given to patients with porphyria owing to the frequent association of psychiatric symptoms. The other important matter to consider is whether there is any relationship between chronic infection, say of the urine or tonsils, and the attacks of abdominal pain. If so, this must be dealt with suitably.

When such causes are found and can be dealt with, prognosis of porphyria is greatly improved. In general, however, it is worse the earlier it starts and the more

frequent have been the number of previous attacks. It is uncommon to start at 15 years of age, so the diagnosis should be carefully considered here. It is wise not to be too depressing about the prognosis, since many patients live a normal span of life, in spite of occasional recurrences, so long as drug therapy is scrupulously controlled.

Reaction to Vaccines

Q.—*When I immunized my son (now 7½ years of age) with combined diphtheria, whooping-cough, and tetanus prophylactic at the age of 1 year, he showed local and general signs of hypersensitivity. There was local swelling, heat, and tenderness of the thigh, the temperature rose to 103 F. (39.4° C.) and there was general malaise. The same occurred after the second injection four weeks later. I now want to give him polio vaccine. What would you recommend?*

A.—The fact that your son experienced over six years ago a reaction to triple vaccine is not a contraindication to a full course of polio vaccine injections at the usual intervals. Reactions to polio vaccine are rare, and, if they do occur, almost always trivial. The inoculated material contains no serum or other protein to which children may have been previously sensitized. Some cases of reaction have occurred in the past due to penicillin sensitivity, but nowadays penicillin is no longer used in the preparation of polio vaccine. It is, however, a wise precaution, as it is in the administration of all vaccines and antisera, to have adrenaline (1 in 1,000) available for emergency use.

Excessive Axillary Sweating

Q.—*I have a patient who suffers severely from excessive localized sweating in both axillae. It is of sufficient quantity to form into distinct drops, and consequently ruins any clothing that may be worn. It is exaggerated by even one glass of alcohol. Are there any means of preventing or diminishing this worrying symptom?*

A.—Excessive sweating of the axilla can be prevented by dividing the sympathetic nerves which supply the sweat glands. It is not possible to guarantee a perfect dryness, but in most cases, if the operation is adequate, the patients are freed from their miserable existence. In doing the operation it is essential to remove the second to the fifth thoracic ganglia, which can easily be done by a supraclavicular extrapleural approach. In some patients, owing to their anatomical construction, the operation must be done by a transpleural approach necessitating two stages, one for each side.

It must be remembered that the hands of these patients will also be denervated, and, besides being dry, will be warmer than normal. The warmth may be no disability, but the dryness can be a disability for persons using their hands for housework. It should be prevented by the regular use of an efficient skin emollient.

Paracetamol

Q.—*What is the toxicity of paracetamol? Has it any phenacetin-like toxic properties, and are there any clinical contraindications to its continued use?*

A.—Paracetamol is the major metabolic product of phenacetin and it is probably responsible for most of the analgesic action of phenacetin. Paracetamol is an extremely safe weak analgesic; 0.5 g. of it has about the same analgesic effect as tab. codein. co. It has the important advantage over phenacetin and aspirin that it does not cause gastric irritation, and therefore it may be used safely in patients with dyspeptic symptoms. Unlike phenacetin also it does not cause sulphaemoglobinaemia even when given over a long period. Very large doses may cause some haemolysis, but no serious toxic effects have been reported from its use in ordinary therapeutic doses of 0.5–2 g. It can safely be given to any patient.

NOTES AND COMMENTS

Purpura Associated with Thalidomide.—Dr. J. H. LONGSTAFF (Blunsdon, Wilts) writes: In the *Journal* ("Any Questions?" July 8, p. 125) a question was asked about the possibility of thalidomide causing a purpuric rash, and in the answer mention was made of the reported neurological toxic effects but that no cases of blood dyscrasias had been reported. The following case report, which presents both neurological and purpuric features, may therefore be of interest. A woman, aged 28, with a long history of asthma and a past history of eczema and possibly rheumatic fever, had been taking "asmaval" tablets (thalidomide 12.5 mg.; ephedrine hydrochloride 20 mg.) intermittently over a period of three to four months. While taking the tablets she developed a vague malaise, with weakness and paraesthesia in the arms, a purpuric rash over the extensor surfaces of the legs, and a painful effusion in the left knee-joint. Some hours later she developed vertigo with a "rushing sound in the ears," but her general condition remained good. No other cause for her symptoms could be determined, and she had taken ephedrine in various forms for many years without mishap. Her blood picture remained normal: microscopy N.A.D., Hb 98% (14.5 g.%), clotting time four minutes, W.B.C. 9,300 per c.mm. (polymorphs 77%, lymphocytes 20%, monocytes 3%, platelets 471,000). It would appear, therefore, that the disorder was essentially allergic in nature. On withdrawal of the drug the toxic effects disappeared within ten days, the neurological signs being the most persistent.

Fainting During Dental Treatment.—Dr. E. P. TURNER (Manchester 13) writes: In cases similar to that described under "Any Questions?" (August 5, p. 397), where the patient is known to be prone to faint during dental treatment, I find that this occurrence can be prevented by tilting back the dental chair at the commencement of each session of treatment. Treatment on the upper jaw can be carried out with the patient's feet above the level of his head; for operations on the lower teeth this position presents technical difficulties, but the patient is kept as near horizontal as possible. It would be inexcusable, on this account, to extract the tooth of the patient described in your columns, as suggested by your questioner, as an alternative to conservative treatment.

OUR EXPERT replies: Laying the patient flat is part of the accepted method of treating a vaso-vagal fainting attack when once this has occurred, and threatened faints in the dental chair can no doubt often be controlled in this way. Emotion, however, is almost certainly the trigger mechanism of a vaso-vagal attack in the dental chair, as shown by Professor Sharpey-Schafer and Dr. Hayter,[1] and it seems important, therefore, to try to treat the cause by effective sedation and full local anaesthesia. As Dr. Turner points out, extraction rather than crowning would probably be bad dental practice in this case, but, quite apart from this, it would probably also fail to avoid a faint, since the emotion connected with the extraction would be likely once again to trigger off a vaso-vagal fainting attack unless careful preparation of the patient with suitable sedatives had been carried out beforehand.

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1 Sharpey-Schafer, E. P., and Hayter, C. J., *Brit. Heart J.*, 1958, 20, 583.

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